Chapter 8. Cardiovascular Health Effects

A summary of the conclusions regarding the evidence of a causal association between ETS exposure and cardiovascular effects from the 1997 OEHHA report and this update are provided below in Table 8.0. These conclusions are based on a weight of evidence approach. In summary, there is evidence that exposure to ETS causes coronary heart disease. In addition, there is evidence suggestive of an association between ETS exposure and alterations in various measures of vascular function as well as stroke.

Table 8.0 ETS and cardiovascular health: comparison of OEHHA (1997) and Update

Outcome	# Studies 1997	#Additional Studies in Update	Finding OEHHA 1997 Evidence of causal association?	Findings Update Evidence of causal association?
CHD	18	8[a]	Conclusive	Conclusive (strengthened)
Altered vascular properties[b]	6	8[c]	Suggestive	Conclusive (strengthened)
Exercise tolerance	4	0	Suggestive	Unchanged
Stroke	0	1	Not assessed	Suggestive

[a]Includes five epidemiological studies and three meta-analyses; [b] Including aortic distensibility and reactivity, intima-media thickness, lesion formation, platelet aggregation, and altered blood lipids. [c]Includes six epidemiological and two animal studies

8.0. Introduction

The association between coronary heart disease (CHD) and exposure to environmental tobacco smoke (ETS) was examined in OEHHA's 1997 report (Cal EPA, 1997). The following is from the conclusion presented in that report:

> "In summary, the epidemiological data, from prospective and case-control studies conducted in diverse populations, in males and in females, in western and eastern countries, are supportive of a causal association between ETS exposure from spouses and CHD mortality in nonsmokers."

This chapter reviews the relationship between cardiovascular disease and ETS exposure in light of the epidemiological studies, meta-analyses and related research published since the 1997 report. Various contributing conditions and endpoints of cardiovascular disease were measured in the studies reviewed below, including myocardial infarction (MI), ischemic stroke, coronary flow velocity reserve (CFVR), flow-mediated dilatation (FMD), aortic responsiveness and elasticity, arterial intima-media thickness (IMT), and high and low density lipoprotein-cholesterol (HDL-C, LDL-C).

ETS has been associated with a number of measurable physiological and biochemical changes in exposed individuals. These include increases in blood levels of atherogenic lipids and arterial wall thickness, decreases in aortic elasticity, endothelial responsiveness, blood levels of HDL-C and exercise endurance. It has also been associated with platelet activation and enhanced plaque growth. These effects are thought to be responsible, at least in part, for the increased risks of CHD, ischemic stroke and sudden death associated with exposure to cigarette smoke.

8.1. Description of Recent Studies

This section begins with a review of three meta-analyses relating the risks of CHD to ETS exposure in the home and/or workplace (He *et al.*, 1999; Law *et al.*, 1997; Wells, 1998). MI is the endpoint in the subsequent two studies by Rosenlund *et al.* (2001) and Ciruzzi *et al.* (1998), followed by studies of the atherogenic effects of ETS in children (Moskowitz *et al.*, 1999) and mice (Gairola *et al.*, 2000), and the role of ETS in stroke (Bonita *et al.*, 1999). A series of studies of the relationship between endothelial properties and function, and cardiovascular risk provide a theoretical mechanistic basis to explain some of the associations between ETS exposure and CHD outcomes.

Table 8.1 Summary of Cited Studies

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
He *et al* 1999	Meta-analysis of 18 epi studies of nonsmokers' risk of CHD from ETS 10 Cohort, 8 Case-control	 Men Women Cohort Case-control Work Home 1-19 cig/d > 20 cig/d	CHD incidence 1.22 (1.10; 1.35) 1.24 (1.15; 1.34) 1.21 (1.14; 1.30) 1.51 (1.26; 1.81) 1.11 (1.00; 1.23) 1.17 (1.11; 1.24) 1.23 (1.13; 1.34) 1.31 (1.21; 1.42)	Inconsistent confounder control. All controlled for age and sex. 6 cohort studies controlled for b.p./hypertension, weight/BMI, cholesterol or hyperlipidemia. In 10 studies with control for CHD risk factors, RR = 1.26 (1.16; 1.38; p<0.001). Dose-exposure increase in risk.
Law *et al.* 1997	Meta-analysis of 19 studies of ischemic heart disease in never- smokers living with vs without smoker. N=6,600 events	Men and Women + ETS Adj for diet	Ischemic heart disease risk 1.30 (1.22; 1.38) 1.23 (1.14; 1.33)	Estimated that diet alone of nonsmokers living with smokers increased risk 6%. Thus RR adjusted for diet is 1.30/1.06 = 1.23
Wells 1998	Meta-analysis of workplace ETS and CHD in 8 studies 1,699 cases	Workplace Top 3 studies + next 4 + ACS	RR for CHD 1.50 (1.12; 2.01) 1.35 (1.09; 1.67) 1.18 (1.04; 1.34)	Ranked studies by quality of ETS exposure data, then by control for confounders. Am. Cancer Society Study.
Rosenlund *et al* 2001 Sweden	Rated risk of MI from ETS at work and/or from spouse in 45-70 yr olds. 344 nonfatal MI, 677 pop controls	Spouse < 20 cig ≥ 20 cig wrk+spouse 0-17 hr-yr 18-41 hr-yr 42-89 hr-yr > 90 hr-yr after ETS stop > 16 yr 7-16 yr 1 - 6 yr < 1 yr	OR for MI 1.02 (0.73; 1.42) 1.58 (0.97; 2.56) 0.70 (0.43; 1.15) 1.22 (0.80; 1.88) 1.27 (0.83; 1.95) 1.55 (1.02; 2.34) 0.92 (0.58; 1.44) 1.11 (0.70; 1.74) 1.30 (0.85; 1.98) 1.39 (0.91; 2.10)	ETS exposure associated with MI. Risk increased with dose (# cigs) from spouse and with duration (hr-yrs) from work and spouse. Increased time since cessation of ETS exposure reduced risk. Adjusted for age, BMI, sex, SES, job strain, hypertension, diabetes, diet. Inclusion of previous smokers as never smokers may explain lack of statistical significance.

* Abbreviations: AMI - acute myocardial infarction; BMI – body mass index; BP – blood pressure; CFVR – coronary flow velocity reserve; CHD – coronary heart disease; FMD – flow-mediated dilitation; HDL-C – high-density lipoprotein cholesterol; IMT – intima-media thickness; NS – never smokers; NTG – nitroglycerin; OR – odds ratio; RR – relative risk; SES – socioeconomic status; SHS – secondhand smoke; SS – sidestream smoke.

Table 8.1. Summary of Cited Studies (continued)

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
Ciruzzi *et al.*, 1998 Argentina	Case-control study of home ETS and acute MI. 336 never smokers with first MI vs 446 never smokers without.	1 relative smoked men women both	OR for AMI 1.89 (1.13; 3.18) 1.54 (0.95; 2.51) 1.68 (1.20; 2.37)	Compared ETS of nonsmokers hospitalized for 1st MI vs those hospitalized for non-cardiac disease.
Enstrom and Kabat 2003	Prospective cohort study of ETS and CHD deaths in CPS-I. 35,561 never smokers	Spousal ETS ever ETS Cig/day 1-9 10-19 20 21-39 ≥ 40	CHD death 0.94 (0.85; 1.05) Male CHD death 0.98 (0.78; 1.24) 0.82 (0.66; 1.02) 0.89 (0.70; 1.13) 1.13 (0.76; 1.68) 1.24 (0.70; 2.19)	Suggestion of exposure-response for death by CHD in men but not women. Effect not statistically significant for either gender.
Moskowitz *et al.* 1999	Cross-sectional study of CHD risk factors in pubertal children vs ETS, race, sex in 408 twin pairs 11-15 yr	Family ETS exposure ETS No ETS ETS No ETS ETS + family history CHD No CHD	Level (mmol/ml) HDLC 1.19 ± 0.22 1.26 ± 0.28 $HDLC_2$ 0.30 ± 0.16 0.35 ± 0.20 HDLC 1.18 ± 0.23 1.25 ± 0.23	Lower levels of HDL-C and subfraction 2 (HDL_2-C) in kids from smoking families ($p \leq 0.01$, $p \leq 0.001$, resp). Even lower HDL-C in smoking families with CHD history ($p<0.001$).
Knight-Lozano *et al.*, 2002	Laboratory exposure of atherosclerosis-prone mice to second hand smoke (SHS). Mitochondrial damage and lesions measured in aorta.	$ApoE^{-/-}$ mice 30 mg/m^3 21d " 42d Mitochondrial lesions 1 mg/m^3 42d 30 mg/m^3 42d	Aortic lesion area +76% vs no SHS +156% " Lesions/16 kilo-bases 1.3 6.0 $p<0.001$	Significant increase in aorta lesion area ($p<0.05$), and in mitochondrial DNA damage after SHS exposure. Hypercholesterolemia increased SHS damage to mitochondria and aorta wall.

* Abbreviations: AMI - acute myocardial infarction; BMI – body mass index; BP – blood pressure; CFVR – coronary flow velocity reserve; CHD – coronary heart disease; FMD – flow-mediated dilitation; HDL-C – high-density lipoprotein cholesterol; IMT – intima-media thickness; NS – never smokers; NTG – nitroglycerin; OR – odds ratio; RR – relative risk; SES – socioeconomic status; SHS – secondhand smoke; SS – sidestream smoke.

Table 8.1. Summary of Cited Studies (continued)

Reference Area	**Study description**	**Exposure to smoke**	**Outcome and RR, OR (95% CI)**	**Comments***
Gairola *et al*. 2001	Laboratory exposure of atherosclerosis-prone mice to side stream smoke (SS). Lesions and lipids measured in aorta.	 SS Control SS Control	Lesion area 33 ± 11% 10 ± 8% Cholesterol 7 wk 718 ± 61 mg/dl 553 ± 26 mg/dl	Significant increase in area of aorta covered by lesion after SS exposure ($p<0.001$). Transient increase in plasma cholesterol at 7 wks in SS mice but back to control levels by 14 wks.
Bonita *et al*. 1999 New Zealand	Population-based, case-control study of stroke vs smoking status. Stroke: men 279, women 242. Ctrl: 1,851. 35-74 yr	Status: Non (ns) Men ns Women ns Smoker vs ns +/-ETS ns-ETS	Stroke OR 1.82 (1.34; 2.49) 2.10 (1.33; 3.32) 1.66 (1.07; 2.57) 4.14 (3.04; 5.63) 6.33 (4.50; 8.91)	Adjusted for age, sex, heart disease, hypertension (not diet). Source of ETS not delineated. Higher OR for stroke in men. Exclusion of ETS-exposed non-smokers (ns) in reference group increases smokers' stroke OR.
Stefanadis *et al*. 1998	Measured aortic distensibility in men during cardiac catheterization for chest pain	Smokers: 16 passive 16 active 16 sham	Decrease in dispensability 21% $p<0.001$ 27% $p<0.001$ 0	5 min smoke exposure caused significant reduction in aortic elasticity in both passive and active smokers vs. sham. Recovery seen in passive group 15 min after cessation.
Howard *et al*. 1998 U.S.	Longitudinal study of current, past and passive smokers and change in Initma-Media Thickness (IMT) over 3 yrs. n = 10,914 adults	Smokers: never-ETS never+ETS Past – ETS Past + ETS Current	Progression rate 25.9 ± 2.1 μm/3 yr 31.6 ± 2.0 " 32.8 ± 2.7 " 38.8 ± 2.3 " 43.0 ± 1.9 "	After adjusting for cardiovascular risk factors, lifestyle and demographics, ETS increased progression by 5.9 μm/3yr. No relationship between IMT progression and number of hours exposed.

* Abbreviations: AMI - acute myocardial infarction; BMI – body mass index; BP – blood pressure; CFVR – coronary flow velocity reserve; CHD – coronary heart disease; FMD – flow-mediated dilitation; HDL-C – high-density lipoprotein cholesterol; IMT – intima-media thickness; NS – never smokers; NTG – nitroglycerin; OR – odds ratio; RR – relative risk; SES – socioeconomic status; SHS – secondhand smoke; SS – sidestream smoke.

Table 8.1. Summary of Cited Studies (continued)

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
Otsuka *et al* 2001 Japan	Measured CFVR (coronary flow velocity reserve) by Doppler echocardiography in active and passive smokers before and after 30 min passive smoke.	Nonsmokers Smokers Nonsmokers Smokers	Mean CFVR Before ETS 4.4 ± 0.91 3.6 ± 0.88 p=0.02 After 30 min ETS 3.4 ± 0.73 p<0.001 3.3 ± 0.74 p=0.83	Passive smoke sig. reduced CFVR in nonsmokers and to same level as in active smokers. No sig differences between groups in age, heart rate, b.p., cholesterol, triglycerides and HDL. 15 smokers, 15 non-smokers, men, 27± 4 yrs
Woo *et al* 2000 China Australia	Tested vascular reactivity of brachial arteries by ultrasound in 20 casino workers exposed to ETS >8 hr/d, 6 d/wk, 9.2 ± 6.1 yr vs. 20 Ctrls	Controls Workers Mean diff	Flow-mediated dilatation (FMD) 10.6 ± 2.3% 6.6 ± 3.4% 4% CI 3-5.4% p<0.001	Gender and age matched. BP, medical history, BMI, lipid and cholesterol levels (HDL, LDL). Passive smoking strongest predictor of impaired FMD $R^2 = 0.75$, F = 6.1, p=0.0001
Raitakari *et al.*, 1999 Australia	Cross-sectional study of effects of current and past ETS on flow-mediated dilation (FMD) in 3 x 20 adults 15-39 yr	Status: Never Past ETS ETS	FMD (%) 8.9 ± 3.2 5.1 ± 4.1 p<0.01 2.3 ± 2.1 p<0.01	ETS exposure decreased FMD (p<0.001). Quitting ETS improved FMD vs current ETS (p<0.01) but still worse than never ETS (p<0.01). Control for bp, dyslipidemia, heart disease, diabetes, age and sex. No gender differences.
Sumida *et al.*, 1998	Measured diameters of coronary arteries after ACh by angiography in women hospitalized for atypical chest pain. 11 never smokers 8 active smokers 19 ETS exposed	Status: Never Active ETS Never Active ETS	% diameter change Distal LAD 13.7 ± 3.4 p<0.05 -27.2 ± 6.0 p<0.01 -22.3 ± 4.1 p<0.01 Distal LCX 9.7 ± 3.4 p<0.05 -22.4 ± 4.0 p<0.01 -17.3 ± 2.9 p<0.01	ACh caused dilation of distal segments of left descending and left circumflex arteries in never smokers but constriction in ETS and active smokers. In all groups, NTG increased diameter. Suggests active and passive smoke exposure damages endothelium.

* Abbreviations: AMI - acute myocardial infarction; BMI – body mass index; BP – blood pressure; CFVR – coronary flow velocity reserve; CHD – coronary heart disease; FMD – flow-mediated dilitation; HDL-C – high-density lipoprotein cholesterol; IMT – intima-media thickness; NS – never smokers; NTG – nitroglycerin; OR – odds ratio; RR – relative risk; SES – socioeconomic status; SHS – secondhand smoke; SS – sidestream smoke.

Table 8.1. Summary of Cited Studies (continued)

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
You *et al*. 1999 Australia	Case-control study of ischemic stroke in ex, never, current smokers living with vs. without smoker n = 452	Spouse: Ever 1-20 cig/d ≥ 20 cig/d Ever 1-20 cig/d ≥ 20 cig/d	OR: NS group 1.70 (0.98; 2.92) 1.55 (0.83; 2.88) 1.91 (0.94; 3.88) Whole group 2.03 (1.33; 3.10) 1.72 (1.07; 2.77) 2.59 (1.51; 4.47)	452 cases of first time ischemic stroke vs. age-, sex-matched ctrl. Incl. current, ex, never smokers, parental & spousal exposure. Adj for smoking status, heart disease, hypertension, diabetes, education.

* Abbreviations: AMI - acute myocardial infarction; BMI – body mass index; BP – blood pressure; CFVR – coronary flow velocity reserve; CHD – coronary heart disease; FMD – flow-mediated dilitation; HDL-C – high-density lipoprotein cholesterol; IMT – intima-media thickness; NS – never smokers; NTG – nitroglycerin; OR – odds ratio; RR – relative risk; SES – socioeconomic status; SHS – secondhand smoke; SS – sidestream smoke.

He et al. (1999) conducted a meta-analysis of 18 epidemiological studies (10 prospective cohort, 8 case-control) relating ETS exposure and coronary heart disease (CHD). From these studies, overall nonsmokers exposed to ETS had a pooled relative risk (RR) of CHD of 1.25 (95% CI 1.17-1.32; p<0.001) compared to nonexposed nonsmokers. The cohort studies included (Hirayama, 1990; Garland *et al.,* 1985; Svendsen *et al.,* 1987; Butler, 1988; Sandler *et al.,* 1989; Hole *et al.,* 1989; Humble *et al.,* 1990; Steenland *et al.,* 1996; and Kawachi *et al.,* 1997). The analysis by He *et al.* (1999) excluded three potentially relevant studies: (Tunstall-Pedoe *et al.,* 1995), because it was a cross-sectional survey; (Layard, 1995), as it did not provide valid data on passive smoking, and the case and control groups were not comparable; and (LeVois & Layard, 1995), the results of which conflicted with a "more careful" study by Steenland *et al.* (Steenland *et al.,* 1996) of many of the same data from the American Cancer Society Cancer Prevention Study II (ACS-CPSII).

In the cohort studies the outcome measure was MI or death due to CHD and the pooled RR for these outcomes was 1.21 (95% CI 1.14-1.30), with mean follow-up periods ranging from 6 to 20 years. The case-control studies included four that assessed ETS exposure from spouse and/or children (Lee *et al.,* 1986; He, 1989; La Vecchia *et al.,* 1993; Ciruzzi *et al.,* 1998) and another four that also included ETS exposure from work (Jackson, 1989; Dobson *et al.,* 1991; He *et al.,* 1994; Muscat & Wynder, 1995). In the case-control studies, the pooled estimated risk (odds ratio; OR) for CHD was higher at 1.51 (95% CI 1.26-1.81) than in the cohort studies. The RR was similar in men, 1.22 (95% CI 1.10-1.35), and women, 1.24 (95% CI 1.15-1.34). There was no significant difference between those exposed to ETS at home (1.17; 95% CI 1.11-1.24), or in the workplace (1.11; 95% CI 1.00-1.23). A dose effect was also suggested with the pooled RR for nonsmokers exposed to 1-19 cigarettes/day of 1.23 (95% CI 1.13-1.34), increasing to 1.31 (95% CI 1.21-1.42) with exposure to ETS from >20 cigarettes/day.

The main limitation of this work is that control for confounders and effect modifiers was inconsistent across studies. Age and sex were controlled in all cohort studies, but only six controlled for blood pressure or hypertension, weight or BMI, serum cholesterol or hyperlipidemia. However, the pooled risk estimate calculated from the 10 studies, case-control and cohort, that controlled for important CHD risk factors, was not much different (1.26; 95% CI 1.16-1.38; p<0.001), suggesting that the effects of confounding factors were minimal. In addition, He *et al.* found that different combinations of studies, which included only peer-reviewed studies or used death or MI as the outcome measure, or which eliminated an outlier study, gave similar pooled RRs in the range of 1.24-1.26. In all cases the ETS effect was significant ($p<0.001$).

Law et al. (1997) conducted a meta-analysis of 19 published studies of the risk of ischemic heart disease in never-smokers living with smokers versus with nonsmokers. Also included were five large prospective studies of active smoking and ischemic heart disease, studies of smoking and platelet aggregation, and studies relating smoking and diet. They derived a relative risk of ischemic heart disease at age 65 for ETS exposure of 1.30 (95% CI 1.22-1.38; $p<0.001$), similar to the extrapolated risk at age 65 from smoking one cigarette a day: 1.39 (95% CI 1.18-1.64; $p<0.001$). This extrapolation implies that the effects from ETS and active smoke exposure are qualitatively similar, a point which is not certain. From cohort studies in which diet was evaluated, dietary differences between nonsmokers who lived with a smoker versus those who did not were estimated to account for an excess ischemic risk of 1-2%. Thus, adjusted for diet, specifically a lower consumption of fruits and vegetables in smoking households, the passive smoker's risk of developing ischemic heart disease dropped to 1.23 (95% CI 1.08; 1.40). Summary estimates were similar for men and women in both cohort and case-control studies.

Platelet aggregation has been suggested as a plausible mechanism to account for the disproportionate risks of CHD associated with ETS versus active smoking. Law *et al.* (1997) reviewed data from the Caerphilly collaborative heart disease study (Elwood *et al.,* 1991) and found a linear association between the risk of ischemic heart disease and platelet aggregation. It was estimated that an increase of one standard deviation (SD) in platelet aggregation was associated with a relative risk of 1.33 (95% CI 1.19-1.48; $p<0.001$). It should be noted, however, that the SDs associated with the relative risk estimates were relatively large. From another series of studies comparing platelet aggregation in non-, passive- and active-smokers, ETS exposure resulted in an increase in platelet aggregation of 1.03 SD while active smoking caused an increase of 1.25 SD. Based on the linear relationship mentioned above this translates into an associated immediate relative risk of ischemic heart disease of 1.34 (95% CI 1.19-1.50) for passive smokers and 1.43 (95% CI 1.24-1.63) for active smokers. While smoke exposure alters platelet sensitivity to aggregation-inducing or inhibiting compounds, and altered platelet aggregation is associated with an immediate risk of IHD, platelet aggregation per se does not appear predictive of long-term ischemic risk (Elwood *et al.,* 2001).

This study has been criticized for excluding a study by Layard (1995) which found no increased risk of ETS from spousal smoking. However Layard included ever-smoking versus using only current-smoking spouses. In the larger studies, risk estimates from exposure to current-smoking spouses tend to be higher than from ever-smokers as the latter group includes ex-smokers. Cessation of exposure to spousal ETS in the latter cases would be expected to alter risk estimates. Alternatively, the increased risk of ischemic heart disease may be more related to an acute versus a chronic effect of ETS exposure in which ETS exacerbates underlying cardio-vascular conditions.

Wells, 1998. Most studies of passive smoke exposure concentrate on ETS exposure in the home environment. However, for many people, the workplace is a significant source of exposure. Wells (1998) evaluated and ranked seven studies that addressed the pooled relative risks (RR) of CHD from workplace ETS exposure. Ranking was determined primarily on the quality of the passive smoking history (duration, intensity and frequency) and secondarily on the extent of adjustment for various confounders. Based on these criteria, the top three studies were He *et al.* (1994); Kawachi *et al.* (1997); and Butler (1988), from which Wells estimated a RR for CHD of 1.50 (95% CI 1.12-2.01) for both sexes combined. The next four studies reported passive smoking history only as either exposed or not exposed. There was less extensive control for confounders and less information on data sources (surrogates vs direct interviews). Inclusion of these studies brought the RR down to 1.35 (95% CI 1.09-1.67). While the American Cancer Society (ACS) study analyzed by Steenland *et al.* (1996) was the largest, it was ranked last for this analysis due to the poorer quality of the data regarding workplace exposure history. Its inclusion brought the combined RR to 1.18 (95% CI 1.04-1.34). Even at this level, there was a statistically significant risk of CHD from workplace ETS exposure that is similar to the RRs reported for home ETS exposure. Thus, refinement of exposure estimates resulted in increased RR reported for ETS exposure and CHD. The similarity in risks associated with work versus home exposure was also observed by He *et al.* (1999).

In an analysis of workplace exposure, the potential for confounding by diet is diminished, as coworkers are less likely to share the same dietary habits as are people living in the same household. The similarity in the RRs associated with home and work ETS exposure thus suggests that while dietary effects cannot be excluded, dietary effects alone cannot explain the excess CHD risk.

This analysis excluded LeVois and Layard's (1995) study of ACS CPS-I data due to uncertainty about the inclusion or exclusion of subjects in favor of the "more detailed analysis" by Steenland *et al* (1996) of the ACS CPS-II data. Layard's 1995 study based on the National Mortality Followback Survey was also excluded as it contained a disproportionate number of blacks, Native Americans and young people who had died of ischemic heart disease. In this case ETS exposure was reported by spouses or surrogates on mailed questionnaires rather than from direct interviews. Neither of these studies found an association between ETS exposure and heart disease. Wells estimated that with inclusion of Layard's data, the combined RR for mortality would drop from 1.23 to 1.17 (95% CI 1.10-1.25). He also calculated that for combined morbidity and mortality, the risk would drop from 1.28 to 1.22 (95% CI 1.15-1.29); however it is not clear how these numbers were derived.

There are other reasons for excluding the analysis by LeVois and Layard (1995), as pointed out by Brown (1998). In their analysis, Le Vois and Layard included ex-smoking spouses as though they had smoked throughout the 13-year period of the study. There was also no evaluation of how many smoking spouses quit during that period. Given the reduction in risk associated with the cessation of smoke exposure (U.S.-DHHS, 1990), the inclusion of former smokers among smoking spouses would diminish the apparent effect of ETS exposure. Also, since the mean age of the subjects at the start of CPS-I was 55, it is reasonable to expect a number of CHD-related deaths among the nonexposed subjects during the 13-year followup. Any effect of ETS exposure would be expected to be reflected in the time-to-CHD events in the exposed versus the non-exposed groups. It is not clear that the analysis conducted by LeVois and Layard was able to detect a difference in the mean time-to-event for ETS-exposed versus nonexposed subjects. The inclusion of former smokers with current smokers is also a problem with the study by Layard (1995). In addition, cases in Layard's study were on average 6-7 years older at death than controls. Since age is a recognized risk factor for CHD, the exposed and control groups would not have been exposed to the same age-related risks. Had the controls lived the same length as cases, whether or not the controls developed CHD would significantly affect the estimates of relative risk.

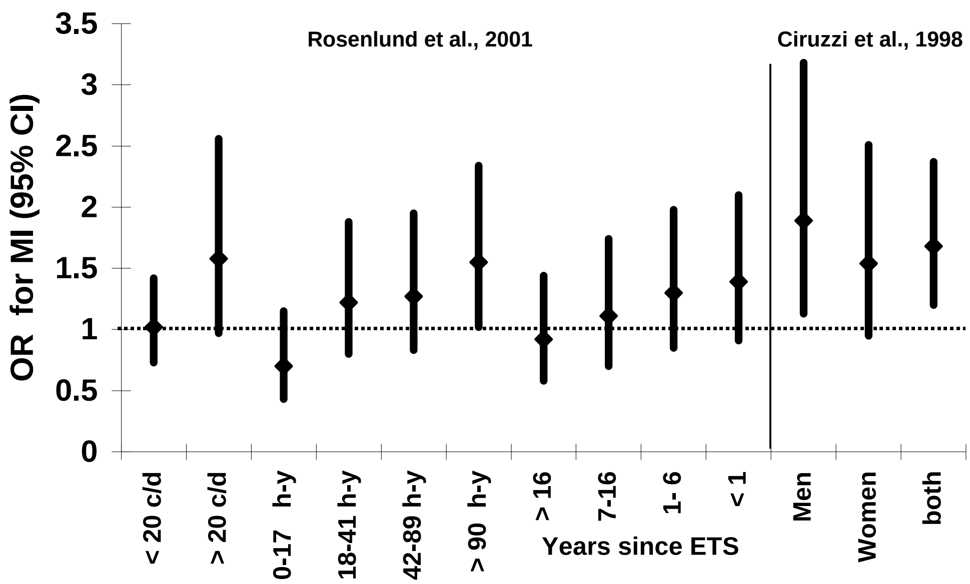
Rosenlund et al. (2001) evaluated the risk of myocardial infarction (MI) associated with ETS exposure at work and/or from spousal smoking among participants in the Stockholm Heart Epidemiology Program (SHEEP). Data from 334 non-fatal never-smoking MI cases and 677 population controls ages 45-70 yrs (avg 62.6 ± 6.6 yrs) in Sweden were collected by postal questionnaire and telephone followup. The collected data included ETS exposure, age, gender, body mass index (BMI), socioeconomic status, job strain, hypertension, diet and diabetes. The odds ratios (OR) for MI after adjustment for these factors (sexes combined) showed an exposure-response relationship with the number of cigarettes smoked by the spouse. The risk of MI from combined ETS exposure from work and spouse, expressed in hour-years, also showed an exposure-response relationship. (1 hour-year = 365 hrs or the equivalent exposure duration of one hr/d for one year) In addition, there was a higher risk from recent exposure, which decreased with increasing years since last exposure at home or work (Fig. 8.01).

Except at the highest exposure duration, the confidence intervals reported include no effect. However, this study defined never smokers as "…subjects who had never smoked regularly for at least a year…". As a result, the control group may have included previous smokers and people who smoke intermittently, the inclusion of whom might tend to diminish any apparent effects due to ETS exposure and make the OR estimates artificially low.

The participation rate in the SHEEP study was relatively high (≥ 70%) thus minimizing bias due to nonparticipation and differential reporting. Exposure misclassification is also expected to be minor based on data from population validation studies of reported smoking that indicate about 5% misclassification of ever-smokers in the never-smoking category, mainly of light or long-term ex-smokers. The misclassification rate was even lower in case-control studies in which 1.25% of "never-smokers" were reported by next of kin to be former regular smokers (Nyberg *et al.,* 1998; Nyberg *et al.,* 1997). In the Rosenlund *et al.* study, recall bias was further minimized by excluding fatal MI cases.

It has been argued that the association between ETS exposure and CHD may be explained by differences in the diets of smoking versus nonsmoking families (Forastiere *et al.,* 2000). To address this concern, Rosenlund *et al.* (2001) adjusted for dietary intake of fat and fiber. This adjustment reportedly did not affect the results. Similarly, dietary cholesterol and blood lipids were considered and reportedly had little or no effect on the analysis.

Figure 8.01 Two Studies of the Risk of Myocardial Infarction in Relation to ETS Exposure



Ciruzzi et al. (1998) conducted a case-control study of the association between exposure to ETS in the home and the risk of acute myocardial infarction (AMI) conducted from 1991-1994 in Argentina. Cases included 336 never-smokers admitted to hospitals for first episodes of AMI with a median age of 66. Those with a history of ischemic heart disease, valvular disease, cardiomyopathy or cardiac surgery were excluded. Controls comprised 446 never-smokers admitted to the same hospitals for acute conditions unrelated to known or suspected risk factors for AMI with a median age of 65. Data were collected during interviews on age, gender, education, diet, alcohol and coffee consumption, socioeconomic status, BMI, presence of diabetes and hypertension, family history of MI, and smoking habits of spouse and children. Serum cholesterol was determined following hospital admission. Odds ratios were calculated for

AMI from multiple logistic regression analyses adjusted for these factors. For men, the OR for AMI when at least one person in the household smoked was 1.89 (95% CI 1.13-3.18), for women 1.54 (95% CI 0.95-2.51), and for both sexes, 1.68 (95% CI 1.20-2.37) (Fig. 8.01). For women, an exposure-response trend with spousal smoking was suggested. An OR of 0.90 (95% CI 0.28-2.86) for spousal smoking of 1-20 cigarettes per day increased to 3.31 (95% CI 0.77-14.17) at >20 cigarettes per day.

The participation rate in this study was high (96%) with good comparability of the recruitment areas for cases and controls. However, while the median ages of both groups were similar, a higher percentage of the cases was over 75 years of age compared to the control group (28.6% vs 17.7%), which may have exaggerated the ETS effect. Since the cases and controls for this study were admitted to hospitals for AMI or other conditions, the applicability of these results to an otherwise healthy population may be somewhat limited. Indeed, the authors found evidence that interaction between ETS exposure and chronic conditions may influence risk for CHD and AMI. The OR for AMI when at least one relative smoked rose from 1.51 (95% CI 1.04-2.19) in the absence of diabetes, to 5.26 (95% CI 2.44-11.36) in its presence. Similarly, hypertension increased the OR associated with ETS from 1.65 (95% CI 1.03-2.65) to 3.28 (95% CI 2.02-5.34), while with hypercholesterolemia the OR went from 1.60 (95% CI 1.08-2.34) to 4.01 (95% CI 2.17-7.40). A family history of MI was found to enhance the ETS effect with ORs increasing from 1.71 (95% CI 1.16-2.53) to 4.08 (95% CI 2.16-7.70). This study thus suggests that individuals with other risk factors for AMI may be especially susceptible to the effects of ETS exposure.

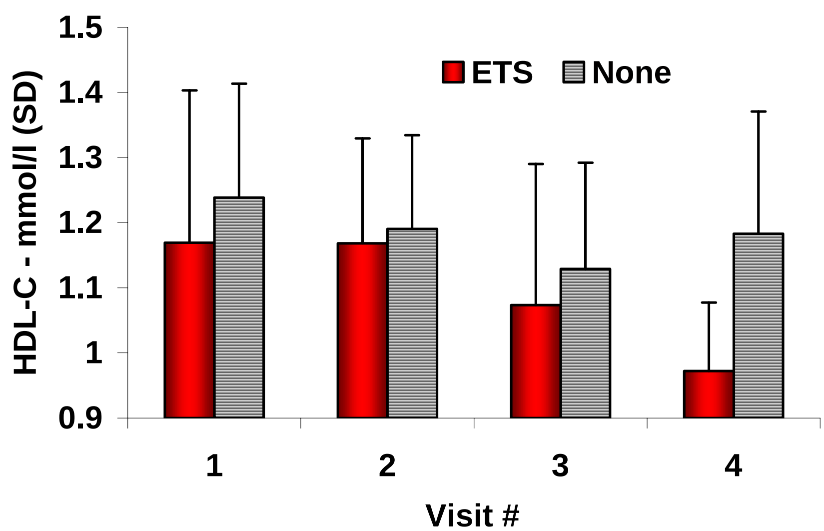
Enstrom & Kabat (2003) examined ETS exposure and long-term mortality from CHD, lung cancer and chronic obstructive pulmonary disease (COPD) in a prospective cohort study of the adult Californians enrolled in 1959 in the American Cancer Society's Cancer Prevention Study (CPS-I). Never smokers married to current or former smokers were compared to never smokers married to never smokers, with the former group subdivided based on the smoking status of the spouse (1-9, 10-19, 20, 21-39, ≥ 40 cigarettes per day). Former smokers were considered in a separate category. The relative risk of death was calculated as a function of the spouse's smoking status and adjusted for age and seven potential confounders at baseline: race, education, exercise, BMI, urbanization, fruit or fruit juice intake, and health status (good, fair, poor, sick).

For CHD among males, there was a suggestion of an exposure response based on ETS from increasing numbers of cigarettes smoked per day by the spouse but the confidence intervals included no effect (Table 8.01).

There are several concerns with this study which are described in the review of Enstrom and Kabat in Section 7.3.2.1. The concerns revolve around potential misclassification of smoke exposure due to the high prevalence of cigarette smoking and thus extensive ETS exposure at the start of CPS-I, and defining ETS exposure based solely on spousal smoking during the first third of the study period . At the time of CPS-I, cigarette smoking was more prevalent, and ETS much more pervasive than it is now. As a result, the control group, defined as non-ETS-exposed based on the absence of spousal smoking, would include individuals with extensive ETS exposure outside the home at work and elsewhere. Analyses were adjusted for the factors listed above at baseline and while race, education, exercise, weight, height, and fruit intake reportedly changed little over time, changes in health status or in other lifestyle factors that could affect survival were not included in the adjustment. There was, for example, a large increase between 1959 and 1999 in the proportion of the population using vitamin pills (38.3% and 81.2%, respectively) that may have mitigated the effects of smoke exposure. In addition, the category of current smokers may include intermittent smokers and those who started smoking relatively recently, potentially leading to wide variations in the duration of ETS exposure among never smokers, and a dilution of effects. Thus, while this study does not appear to support a causal role for ETS in CHD mortality, the problems noted above lead to difficulty in interpretation of these study results.

Moskowitz et al,. 1999. Most investigations of the association between CHD and ETS focus on adults. In this study, Moskowitz *et al.* examined how CHD risk factors, passive smoking, gender and race are related in pubertal children. Data were collected during four visits at 18-month intervals from 113 twin pairs from 11-15.5 years of age. Information on family and health histories, smoking, alcohol use, blood pressure, and anthropometrics was collected by questionnaire and during interview. Biochemical assays provided data on blood HDL-cholesterol (HDL-C), LDL-C, and cotinine. HDL-C subfraction 2 (HDL_2-C) was also assessed as most of the variation in HDL-C is due to this subfraction and others have shown that CHD deaths occur more frequently in families with low levels of HDL_2-C (Bodurtha *et al.,* 1987). At the first visit, children with long-term passive smoke exposure had significantly lower HDL-C (visit 1: 1.19 ± 0.22 vs 1.26 ± 0.28 mmol/L; $p \leq 0.01$) and HDL_2-C (0.30 ± 0.16 vs 0.35 ± 0.20 mmol/L, $p \leq 0.01$) than kids from nonsmoking families. In addition, over the course of the four visits, HDL-C significantly decreased among children exposed to ETS compared to children in nonsmoking families ($p \leq 0.001$ for trend; Fig 8.02). The negative effects of passive smoke exposure on HDL-C levels were more pronounced in children of families with a history of cardiac disease versus those without (visit 1: 1.18 ± 0.23 vs 1.25 ± 0.23 mmol/mL; visit 4: 0.98 ± 0.10 vs 1.19 ± 0.18 mmol/mL; p<0.001). This study indicates that in children also, ETS exposure has a deleterious effect on HDL-C levels, a risk factor for CHD. In addition there appeared to be differences in susceptibility to ETS effects related to race, gender and familial history of cardiac disease.

Figure 8.02 ETS Exposure and HDL-C Levels in Children

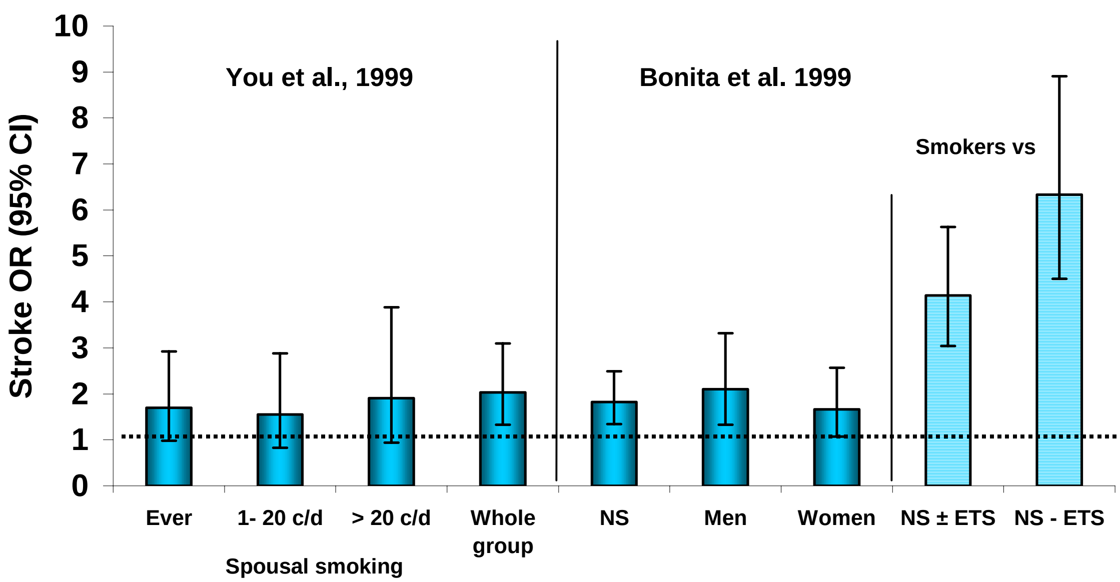


Adapted from: Moskowitz *et al.*, 1999

You et al. (1999) conducted a case-control study in Australia of ischemic stroke in 452 never, former, and current smokers living with smokers compared with a similar number of age and sex-matched neighborhood controls not exposed to ETS. The study group was 59.5% male with a mean age of 59 (SD ± 14.8) years. Parental and spousal smoking were examined but the former had no effect on stroke risk. Among never-smokers exposed to spousal ETS, the odds ratios adjusted for age, gender, hypertension, ischemic heart disease, diabetes, personal smoking and education, were elevated and suggested an exposure-response, but the 95% CIs included unity, consistent with an estimate of no increased risk. On the other hand, the risk for ischemic stroke from spousal smoking for the entire group, including smokers as well as nonsmokers, was significantly elevated with an adjusted OR of 2.03 (95% CI 1.33; 3.10) (Fig 8.03). This suggests that smokers may also be susceptible to ETS. Indeed, when the data for active smokers was stratified according to smoking by the spouse, the OR for stroke for active smokers exposed to spouse's ETS was 1.91 (95% CI 0.90; 4.04) (data not plotted).

Because this was a hospital-based study, selection bias is a concern, especially since the controls were recruited from the community rather than from the hospital. In addition, recruitment occurred in two phases, from 1985 to 1988, and from 1988 to 1992. The latter group contained patients ≤ 55 years of age. Recognizing these weaknesses, the authors suggest that these results, although indicating an association between ETS and stroke, should be regarded as hypothesis generating.

Figure 8.03 Two Studies of the Risk of Stroke and ETS Exposure



Bonita et al. (1999) conducted a population-based case-control study of smoking status versus stroke incidence in first-time stroke victims (279 men, 242 women) compared with 1,851 controls. Cases were taken from the Auckland stroke study, which documented stroke events among the Auckland population in 1991-1992. Trained nurse interviewers administered questionnaires to the stroke victims, or to next-of-kin if the patient had died, to assess age, gender, history of smoke exposure, heart disease, hypertension and diabetes. Odds ratios for stroke incidence among active smokers were derived from comparisons with never-smokers with and without ETS exposure and with never-smokers with no ETS exposure. Active smokers were separated into three groups for analysis based on the number of cigarettes smoked per day (≤ 5, 6-14, ≥ 15). Ex-smokers were included and grouped according to the time elapsed since quitting (< 2, 2-10, >10 yrs). A person was classified as having been exposed to ETS if a household member had regularly smoked cigarettes in their presence or if a co-worker smoked in their presence for more than one year during the prior ten years.

After adjustment for heart disease, hypertension, diabetes, age and sex, ETS exposure among never-smokers was associated with an elevated risk of stroke (OR 1.82; 95% CI 1.34-2.49), which was higher in men (OR 2.10; 95% CI 1.33-3.32) than in women (OR 1.66; 95% CI 1.07-2.57). Compared to all nonsmokers, the risk of stroke for active smokers was high (OR 4.14; 95% CI 3.04-5.63). More importantly, when the reference group included only nonsmokers with no ETS exposure, the OR for stroke among active smokers increased to 6.33 (95% CI 4.50-8.91). This additionally supports an ETS effect in stroke and underscores the importance of reference group selection (Fig. 8.03).

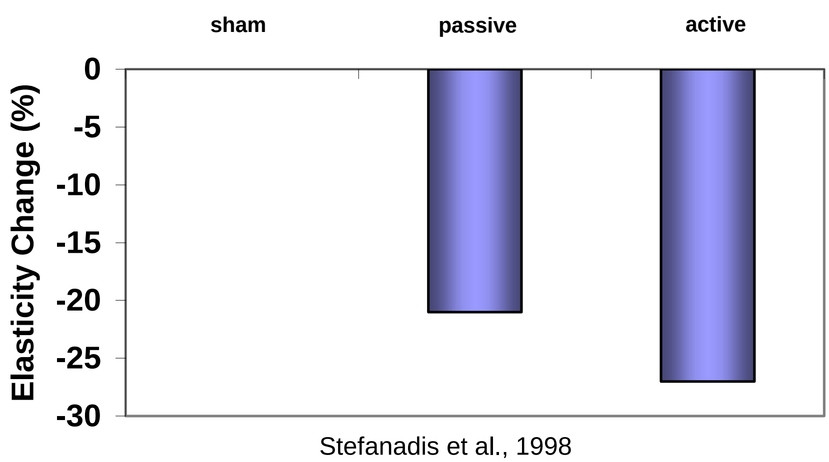
One of the strengths of this study is that all strokes in the Auckland population, fatal and nonfatal, were identified, though there was no differentiation of stroke type or severity in the analysis. The decision to include all nonfatal and fatal cases is important, as passive smoke exposure may be associated with strokes of varying severity from mild to fatal. On the other hand, it limits the study's ability to discern whether ETS exposure is associated with stroke severity.

Limitations of this study include the lack of control for diet. Reporting bias may have resulted from the fact that cases and controls were interviewed in separate years, allowing for exposure to other factors in the intervening time. Also controls were interviewed directly while data for some cases were obtained from a caregiver or next-of-kin. Data on education and socioeconomic status were not included, as 60% of the patients with acute stroke were past retirement age (65-74 yrs). The authors attempted to reduce confounding due to socioeconomic factors by excluding Maoris and Pacific Islanders who tend to be of lower socioeconomic status, and have higher smoking and stroke rates than those of European descent. Another concern with this study is that there may not have been adequate control for age as there were fewer cases less than 55 years of age while only about half of the controls were 55 and older. The reliability of self-reported ETS exposure was not verified biochemically and it is possible that stroke victims and healthy controls reported smoking consumption differently. An attempt to mitigate this potential bias was made by embedding questions regarding smoke exposure among a large number of other questions.

Stefanadis et al., 1998. Loss of arterial flexibility is associated with increased risk of CHD. Stefanadis *et al* studied the association between passive smoking and the elastic properties of the aorta via measurement of instantaneous diameters and pressures in the descending thoracic aorta during and after active, sham and passive smoking. All participants in this study were males (mean 48 ± 10 yr) undergoing diagnostic cardiac catheterization for evaluation of chest pain. The study included 16 nonsmokers (for passive smoke exposure) and 32 current, long-term smokers (≥ 1 pack/d, ≥ 1 yr). For this study the latter group was divided into two groups: 16 active, 16 sham smokers. Passive smokers were exposed to ETS in an exposure chamber with CO levels of 30 ppm for 5 min. Active smokers smoked one filtered cigarette (1 mg nicotine) in 5 min while sham smokers "smoked" one unlighted cigarette for 5 min. Arterial measurements were made at baseline and 1, 2, 3, 4, 5, 10, 15 and 20 min after the start of smoke exposure. Aortic distensibility, which measures vessel diameter as a function of vessel pressure, was used as a gauge of aortic elasticity. Large distensibility values represent improved aortic elasticity while low values indicate deteriorated properties. In this context both passive and active smoking caused decrements in aortic distensibility. Whereas sham smoking did not change distensibility, passive smoking caused a significant 21% decrease from 2.02×10^{-6} to 1.59×10^{-6} cm^2/dyne during the 5 minutes of passive smoke exposure ($p<0.001$) with gradual recovery over the subsequent 15 min to near sham values. Active smoking decreased mean distensibility 27% (from 2.08 to 1.51×10^{-6} cm^2/dyne), and did so more rapidly than did passive smoking, with no recovery during the subsequent 15 min (compared to sham, $p<0.001$) (Fig. 8.04). This study suggests that both active and passive smoking can cause acute deterioration of elastic properties of the aorta and thereby compromise aortic function.

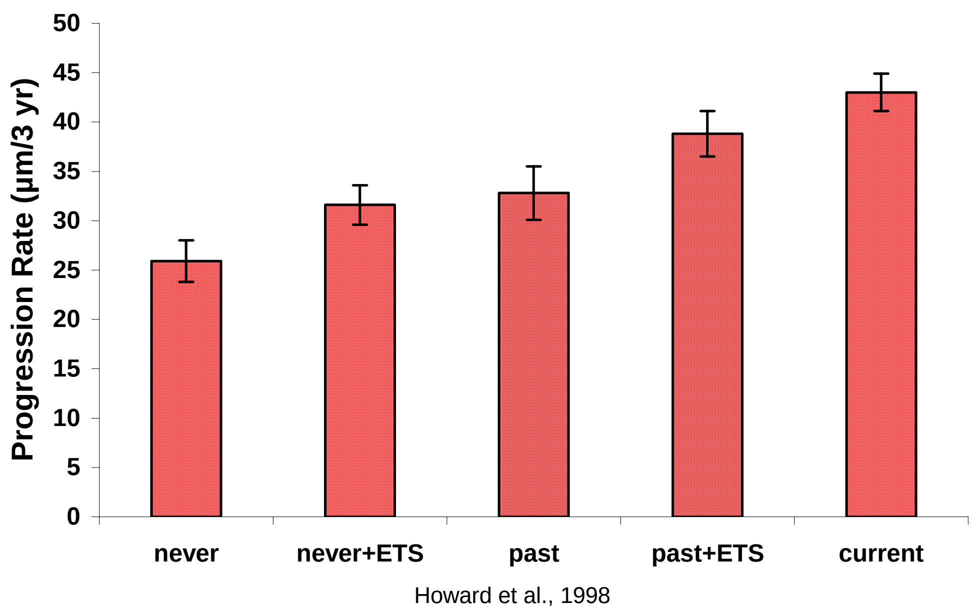
All participants in this study were men, most of whom had coronary heart disease, which limits the generalizability of these results. Although it is unknown whether women and those without CHD would respond in the same way, these data suggest that people with CHD represent a group especially at risk from ETS exposure. Also, since the aorta loses elasticity with age, it is uncertain how younger populations would respond.

Figure 8.04 Loss of Aortic Elasticity with Active and Passive Smoking.



Howard et al. (1998) used data from the Atherosclerosis Risk in Communities Study (ARIC) in a longitudinal assessment of the effects of active and passive smoking on the progression of atherosclerosis over three years. This population based study included 10,914 middle-aged adults (avg age 54 yr). The intima-media thickness (IMT) of carotid arteries was measured by ultrasound at baseline and three years later. Smoking history and ETS exposure were self-assessed by questionnaire. Covariates included blood pressure, LDL-cholesterol, diabetes, fat intake, leisure time activity, education, alcohol use, and body mass index (BMI). The group was divided into 2,956 current smokers, 1,849 past-smokers with ETS exposure (past+ETS), 1,344 past-smokers without ETS exposure (past–ETS), 2,449 never-smokers with ETS (never+ETS), and 2,316 never-smokers with no ETS exposure (never–ETS). Smoking category was the primary independent variable and its relationship to IMT progression was examined with three models. In the Demographic model, the effects of ETS were estimated after adjustment for age, race, sex and baseline IMT. A Risk Factor model adjusted for these factors and for hypertension, HDL-cholesterol, prevalence of CHD and diabetes. The Life-Style model adjusted for all these and for fat intake, education, leisure activity, BMI and alcohol use. All three models showed the same trend. With and without adjustment for cardiovascular risk factors or lifestyle variables, there was a significant progressive increase in wall thickness from never smokers (never-ETS), through those exposed to ETS, to current smokers. After adjustment for life-style, cardiovascular risk factors and demographics (Life-Style model), an increase in IMT progression (in µm/3 yr ± SD) was seen with increasing smoke exposure: never–ETS (25.9 ± 2.1) < never +ETS (31.6 ± 2.0) < past –ETS (32.8 ± 2.7) < past +ETS (38.8 ± 2.3) < current (43.0 ± 1.9) (Fig. 8.05). In this model, ETS increased progression by 5.9 µm over three years (p = 0.01). Current smoking versus never-exposed increased progression by 17.1 µm/3 yrs (43-25.9=17.1), 34.5% (5.9 µm/17.1) of which was attributable to ETS exposure.

Figure 8.05 Progression of Arterial Intima Media Thickness with Smoke Exposure

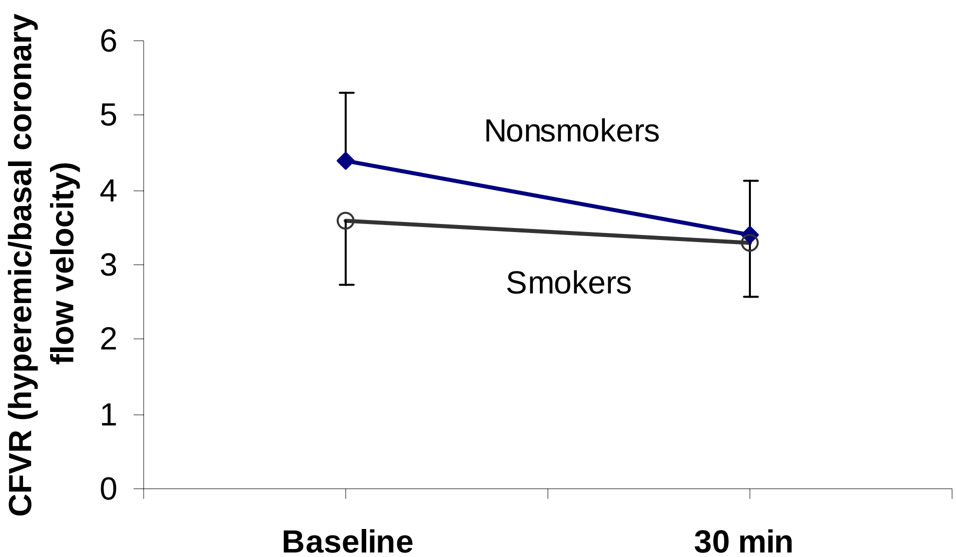


On secondary analysis, no relationship was found between number of hours per week of ETS exposure and IMT progression. This may be due to errors in self-reported exposure estimates, for while data were collected on average weekly exposures to ETS, the exposure environment (home, work, other) was not specified. To the extent that the exposure environment influences the ability to quantify ETS, estimates of the amount of ETS (versus its presence) may include some misclassification error. However, since such misclassification is nondifferential with respect to IMT progression, the effect estimates may be diminished. After control for pack-years of exposure, no significant difference was found between past +ETS and past –ETS. However the similarity of the ETS effect between never-smokers exposed to ETS and past smokers –ETS supports an ETS effect similar to past active smoking.

Otsuka et al., 2001. As a gauge of endothelial function in coronary circulation, coronary flow velocity reserve (CFVR) was measured with transthoracic Doppler echocardiography of the left anterior descending coronary artery. Unlike flow mediated dilatation (see below), which is a measure of endothelial function typically made in brachial arteries, CFVR was based on echocardiographic imaging of coronary arteries to provide an integrated measure of both coronary vascular endothelial function and smooth muscle relaxation. Narrowing of the coronary arteries, or stenosis, was reported by Claeys *et al.* (1996) to be the main determinant of CFVR in patients with myocardial infarction (MI), while Hozumi *et al* (1998) found a CFVR < 2 to be a highly sensitive (92%) and specific (86%) predictor of significant stenosis in the left anterior descending coronary artery. For patients with angina, a CFVR of < 2 was a significant predictor of cardiac events (MI, death, or coronary revascularization) in the year following testing (Chamuleau *et al.*, 2002). Thus decreases in CFVR reflect impaired function in the large epicardial arteries and decreased microcirculation, resulting in a diminished ability of the heart to respond to physiological demands. In the study by Otsuka *et al.*, CFVR was calculated as the ratio of hyperemic velocity (induced by ATP infusion) to basal coronary flow velocity, and reflects the capacity of the arteries to accomodate increased blood flow. Measurements were made in 15 active smoking and 15 nonsmoking males (mean age 27 ± 4 yr) before and after 30 min passive smoke exposure. Smoke exposure occurred in a smoking room where CO levels were monitored (mean 6.02 ppm). Carboxyhemoglobin (COHb) levels were measured before and after exposure. During exposure mean COHb levels (± SD) in nonsmokers rose from 0.40 ± 0.21% to 1.57 ± 0.32%. COHb levels in active smokers before and after exposure were 2.49 ± 1.78% and 2.67 ± 1.79%, respectively. Prior to passive smoke exposure, mean CFVR was significantly higher in non-smokers vs active smokers (4.4 ± 0.91 vs 3.6 ± 0.88, resp., p = 0.02), suggesting compromised endothelial function in the latter group. However, after exposure CFVR was not different between nonsmokers and active smokers (p = 0.83). This result may, in part, be due to small sample size. Passive smoking significantly reduced CFVR in nonsmokers (4.4 ± 0.91 to 3.4 ± 0.73, P<0.001) but not in smokers (3.6 ± 0.91 to 3.3 ± 0.74); in both cases there was no change in heart rate or blood pressure (Fig. 8.06). These data suggest that even a single transient exposure to passive smoke may compromise coronary artery function. No significant differences were seen between groups for age, heart rate, blood pressure, total cholesterol, triglycerides and HDL levels.

This study did not determine which component(s) of tobacco smoke were responsible for the observed effect. However, Tanaka *et al.* (1998) have observed reductions in CFVR in active smokers related to the nicotine content of the cigarettes smoked. The design of the study by Otsuka *et al.* did not allow for an assessment of the long-term effects of passive smoke on CFVR nor a determination of the duration of the effects after exposure cessation. Nevertheless, the results of Otsuka *et al.* suggest that among healthy young adults, ETS exposure may cause endothelial dysfunction of the coronary circulation, an early step in the development of atherosclerosis.

Figure 8.06 Coronary Flow Velocity Reserve after 30 min ETS

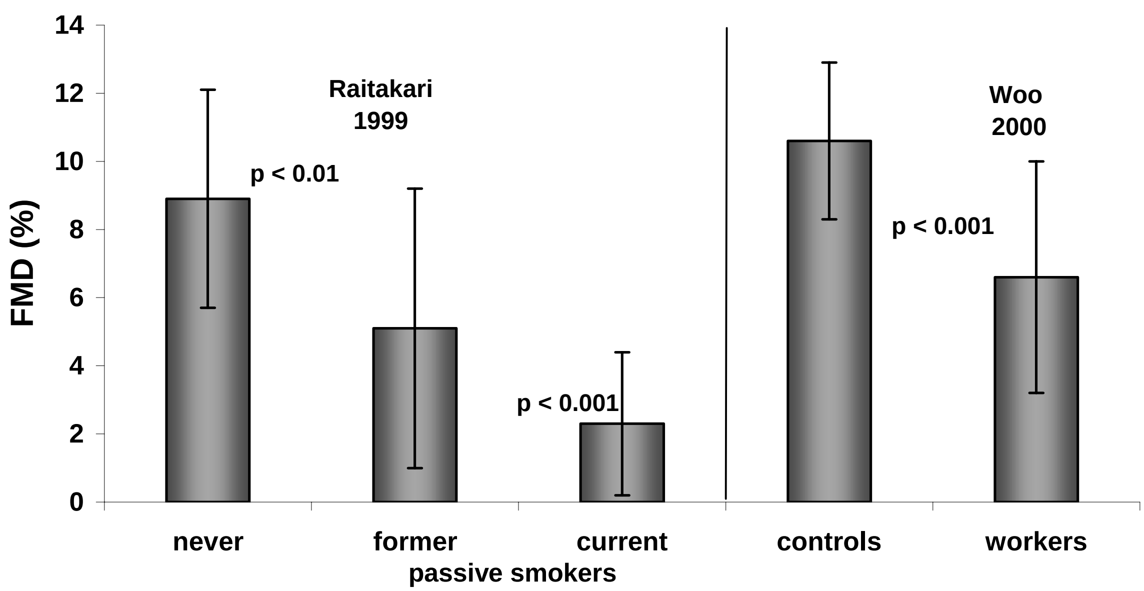


Adapted from Otsuka *et al.*, 2001

Woo et al., 2000. Flow mediated dilatation (FMD) is an endothelium-dependent response to sheer stress caused by increased blood flow. It is largely mediated by the endothelial release of nitric oxide and prostacyclin which cause the relaxation of the underlying smooth muscle. Since an intact endothelium is required for this response, decreases in FMD are taken to reflect decrements in vascular endothelial function and reactivity. In this study, Woo *et al.* evaluated FMD in brachial arteries by ultrasonography in 20 non-smoking casino workers (mean age 36.6

± 7.0 yr) exposed to ETS for over 8 hr/day, 6 day/wk for 2-24 years (mean 9.2 ± 6.1 yrs). FMD was measured following reactive hyperemia caused by pressure cuff release while endothelium-independent dilatation was measured following nitroglycerin administration. Twenty non-exposed controls were matched for age and gender. Age, gender, active smoking, duration of exposure to ETS, blood pressure, BMI, total serum cholesterol (C), HDL-C, LDL-C, degree of hyperemia and vessel size were included as independent variables in the multivariate analyses. In the nonexposed controls, FMD was 10.6 ± 2.3% compared to 6.6 ± 3.4% in passive smokers (mean difference 4%; 95% CI 3-5.4%; p<0.001) (Fig. 8.07). In contrast, nitroglycerin-induced responses were similar in the two groups suggesting that the dysfunction was at the level of the endothelium. Passive smoke exposure was thus associated with impaired FMD which in turn has been related to the extent of coronary disease (1-, 2- or 3-vessel disease) in both CHD and non-CHD patients (Neunteufl *et al.*, 1997). No effect of duration of passive smoking on FMD was seen (p=0.63), however the heavy exposure to ETS, >8 hr/d for over 2 years, may have resulted in a maximal response which would mask a dose-response relationship. After multivariate analysis, passive smoking was the strongest predictor of impaired FMD (ß = -0.59, p = 0.0001), independent of age, gender and other measured variables (model R^2 = 0.75; F value = 6.1, p = 0.0001).

Figure 8.07 Impairment of Flow-Mediated Dilatation with ETS Exposure

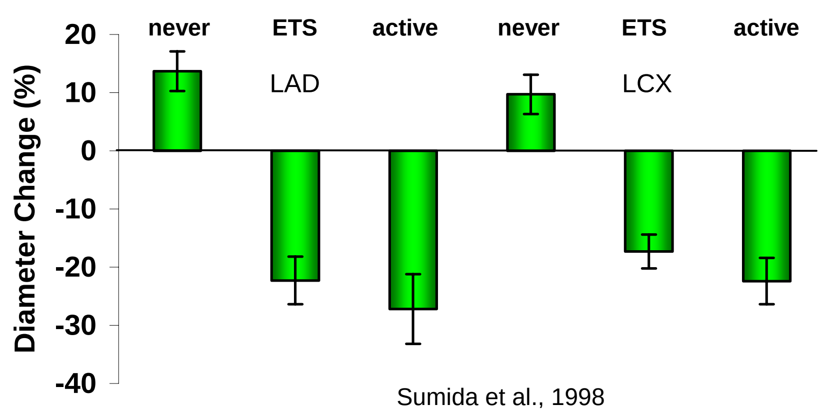


Raitakari et al., 1999. The effects of ETS exposure on vascular reactivity and the potential for recovery following exposure cessation were studied in this cross-sectional study. Reactive hyperemia was induced by pressure cuff release and endothelium-dependent flow-mediated dilatation (FMD) and endothelium-independent (nitroglycerin-induced) dilatation were measured by ultrasonography. The study included 60 young adults (age 15-39 yrs): 20 with no exposure to active or passive smoking (controls), 20 nonsmokers with passive smoke exposure for ≥ 1 hr/d, for ≥ 2 yr, and 20 former passive smokers. Smoke exposure was self-assessed by questionnaire with recent exposure verified by measurement of salivary cotinine. The study controlled for age, sex, dyslipidemia, blood pressure, diabetes, and history of heart disease. Among never smokers, the mean (± SD) FMD was 8.9 ± 3.2%. In former passive-smokers this value was 5.1 ± 4.1%, which dropped to 2.3 ± 2.1% ($p<0.001$) in current passive-smokers (Fig. 8.07). After administration of nitroglycerin, no significant difference was seen among groups for endothelium-independent dilatation. There were also no significant gender differences. In the former passive-smoking group, FMD was most impaired in recent quitters (< 2 yrs; FMD 1.2 ± 1.7%) versus those quitting more than two years previously (FMD 5.8 ± 4.0%; $p \leq 0.05$). Thus ETS exposure was seen to significantly impair vascular responsiveness as measured by FMD and, consistent with other studies, the tissue most adversely affected by ETS exposure was the vascular endothelium. These effects appeared to be at least partially reversible following cessation of smoke exposure. Although limited by its small size and cross-sectional nature, the inverse relationship between ETS exposure and FMD is consistent with a causal role of ETS in CHD.

Sumida et al. (1998) used quantitative coronary angiography to measure diameters of the epicardial coronary artery in response to intracoronary injection of acetylcholine (ACh). The subjects of this study were 38 women admitted to a hospital in Japan for diagnostic cardiac catheterization for evaluation of atypical chest pain. Included were 11 never-smokers not exposed to ETS (mean age 55; range 42-59 yrs), 19 passive smokers (mean age 56; 43-60 yrs) and 8 active smokers (mean age 55; 40-60 yrs). The passive smoking group included life-long nonsmokers with a self-reported history of exposure to ETS at home, work or both for ≥ 1 hr/day for ≥ 10 years. Active smokers were those who smoked ≥ 20 cigarettes per day for > 10 years. Urinary cotinine levels, measured at hospital admission, were not detectable in nonsmokers not exposed to ETS (<5.0 ng/ml). Urinary cotinine levels were 9.1 ± 0.5 ng/ml in passive smokers, and 1,350 ± 60 ng/ml in active smokers. All patients were reportedly free of the following coronary risk factors: hypercholesterolemia (>240 mg/dl), hypertension (>140/90 mm Hg or treatment for hypertension), diabetes mellitus, low HDL-C (<35 mg/dl), family history of premature coronary artery disease, significant stenosis (>25%), coronary spasm, or any other clinically serious disease. There were no significant differences among groups with respect to age, blood pressure, total cholesterol, LDL-C and HDL-C.

Lumen diameters were measured at the proximal, middle and distal segments of the left anterior descending (LAD) and the left circumflex (LCx) coronary arteries by computer-assisted angiography at baseline and after administration of acetylcholine (ACh) and nitroglycerin (NTG). The reponse to treatment was expressed as the percent change in coronary diameter from baseline. In the nonsmokers, ACh significantly dilated the distal segment of the LAD but not the proximal and middle segments. In the LCx, ACh significantly dilated the middle and distal but not the proximal segments. By contrast, in the passive smokers, ACh significantly constricted all segments of the left coronary artery (Fig. 8.08). The degree of constriction in passive smokers was similar to that seen in active smokers. No significant differences were found in ACh-induced constriction between those with light passive smoke exposure (3.7 ± 1.4 hr/day) versus heavy (7.8 ± 2.6 hr/day). There were also no significant differences in response to NTG among active, passive and nonsmokers.

Figure 8.08 Smoke Exposure and Modified Arterial Response to Acetylcholine



In the absence of underlying disease, vasodilation is the normal arterial respose to ACh. This effect is mediated by the endothelium mainly through the release of nitric oxide (NO). On the other hand, ACh causes vascular smooth muscle to constrict. Thus the arterial response to ACh is a result of the balance between the dilator action of endothelium-derived substances, including nitric oxide, and a direct constrictor action of ACh on smooth muscle. The constriction of all segments of the coronary arteries in response to ACh among the patients exposed to smoke, either passively or actively, sharply contrasts with the dilatory response seen in nonsmokers and suggests that the coronary endothelium may have been damaged by smoke exposure. Endothelial damage is further supported by the similarity among all exposure groups to the dilatory effects of NTG, a non-endothelium-dependent response. However, the subjects of this study were admitted to a hospital because of chest pains so it is possible that there were undetected pre-existing conditions other than smoke exposure that may have distinguished the smokers from nonsmokers. In this study there were no significant differences in arterial diameter changes between light and heavy ETS exposure. While this may suggest that the observed effects of ETS on arterial dilatation may saturate at a relatively low exposure levels, the small size of this study precluded a definitive conclusion regarding the exposure-response relationship.

Pope et al., 2001. A characteristic of a healthy cardiovascular system and the associated autonomic nervous system is a high level of heart rate variability (HRV). Decreased measures of HRV have been associated with increased risk of chronic heart failure (Nolan *et al.,* 1998). Pope *et al.* examined changes in both time- and frequency-domain measures of HRV in 16 adults (21-76 yrs) during alternating two-hour periods of exposure to ETS or room air in an airport's smoking and nonsmoking areas. Both areas were monitored for numbers of lit cigarettes, air nicotine, respirable suspended particulates (RSP; > 3μ), and CO. Ambulatory electrocardiograph monitors collected data on all participants during the eight hour experiment for analysis of HRV. Over the eight hour period, nicotine and RSP levels were in the ranges 21-53 $\mu g/m^3$ and 41-166 $\mu g/m^3$, respectively, in the smoking area, and 0-2 $\mu g/m^3$ and 12-43 $\mu g/m^3$, respectively, in the nonsmoking area.

One measure, the standard deviation of normal-to-normal beat intervals (SDNN), correlated most highly with overall measures of HRV and so was used to examine the effect of ETS exposure variables (nicotine, # lit cigarettes, RSP, smoking area indicator) on HRV. Among six models controlling for various covariates, all ETS exposure variables were negatively and significantly ($p<0.05$) correlated with SDNN. Thus the overall effect of ETS exposure in this study was a decrease in cardiac autonomic function, as measured by HRV, that reversed upon cessation of exposure. This study was small and of short duration so it is not known whether chronic ETS exposure would result in chronic depression of HRV. However, the acute effects of ETS on HRV could put susceptible individuals at higher risk of a cardiovascular event.

8.2. Other supportive evidence

Chambless et al. (1997) and Chambless *et al.*(2000) were not specifically designed to examine the effects of smoke exposure on vascular disease; however, they are included here as they substantiate the importance of arterial wall thickness as a risk factor for cardiovascular disease.

Thickening of arterial walls is associated with increased risk of CHD, stroke and death (Bots *et al.,* 1999). In Chambless *et al.* (1997), the mean carotid intima-media thickness (IMT), measured by ultrasonography, was related to CHD incidence during a 4-7 year follow-up among 7,289 women and 5,552 men (45-64 yr). CHD incidents included myocardial infarction (MI), CHD death, and probable CHD based on chest pains, ECG and cardiac enzyme levels. Hazard rate ratios (HRR) were calculated for incident CHD as a function of IMT. After adjusting for age, race, diabetes, cholesterol (C), LDL-C, HDL-C, blood pressure, smoking (pack-years), and alcohol use, an increase in IMT of 0.19 mm (≈ 1 SD) was associated with a HRR for CHD of 1.42 (95% CI 1.24-1.64) in women and 1.18 (95% CI 1.06-1.32) in men. In women, current vs ever smoking had an associated HRR of 3.64 (95% CI 2.30-5.76) while in men this HRR was 2.27 (95% CI 1.53-3.35). Smoking cessation was associated with dramatically decreased HRRs. In female ex-smokers versus never smokers, the HRR was 1.20 (95% CI 0.64-2.27), and the similar comparison for men gave a HRR of 1.17 (95% CI 0.79-1.73). Interestingly, the risk for CHD with increasing IMT increased more rapidly at low IMT values than at higher IMT suggesting a higher sensitivity to smoke in arteries with smaller IMTs at baseline.

The prospective nature of this study made it possible to link IMT measured at baseline with subsequent CHD, thus making it possible to directly examine the risk of CHD incidents as a function of IMT. A limitation of this study was the basing of mean IMTs on a single assessment.

Incomplete sets of ultrasound data necessitated exclusion of some participants and imputation of some IMT measurements for most others using maximum likelihood techniques. This study controlled for most major CHD risk factors; however, some potential confounders such as diet and socioeconomic status were not included. While this study was not designed to specifically examine the effects of smoke exposure on IMT, active smoking was seen to increase the risk of CHD, a relationship that is already well known. The association between IMT and CHD incidence is important in the context of increases in IMT associated with passive smoke exposure reported in other studies (see Howard *et al.*, 1998).

Chambless et al. (2000) conducted a prospective study of ischemic stroke. The mean carotid intima-media thickness (IMT) was measured by ultrasonography and was related to stroke incidence during a 6-9 year follow-up among 7,865 women and 6,349 men (45-64 yr). Hazard rate ratios (HRR) were calculated for incident ischemic stroke as a function of IMT relative to the reference category of 0.6 mm. The HRRs for mean IMT $\geq$ 1 mm compared to $\leq$ 0.6 mm were 8.5 for women (95% CI 3.5-20.7) and 3.6 for men (95% CI 1.5-9.2). A graded increase in the event rate or hazard rate ratio was seen in both men and women. After adjusting for HDL-C, LDL-C, smoking, hypertension, body mass index (BMI), sports activity, diabetes, fibrinogen levels, left ventricular hypertrophy and white blood count, at low IMT, a 0.18 mm increase in IMT gave a HRR for stroke of 1.21 (95% CI 1.05-1.39) in men and 1.36 (95% CI 1.16-1.59) in women. These results suggest that mean IMT is predictive for subsequent ischemic stroke. As in the study on CHD, with spline models the stroke risk reflected in the HRR increased more rapidly at low IMT than at higher IMT. While the results presented here are similar to those above for the incidence of CHD associated with IMT (Chambless *et al.*, 1997), it should be noted that although increased carotid wall thickness played a role in the etiology of stroke, the thickening of the carotid wall as measured in this study was not assumed to be the sole cause of ischemic stroke. Rather it was a surrogate marker for the existence or development of etiologically significant lesions elsewhere. Whereas CHD is due almost exclusively to atherosclerosis, stroke has a mixed etiology that includes degeneration of intracerebral arteries as well as atherosclerosis of the carotid and basilar arteries and the large arteries of the brain.

This study shares the limitations reported above for the ARIC CHD study, including basing of IMTs on single assessments, incomplete sets of ultrasound data requiring imputation of some

IMT measurements and no control for some potential confounders such as diet and socioeconomic status. As with the report above, the effects of smoke exposure on IMT were not addressed; however, these results complement the longitudinal study by Howard *et al* (1998) that specifically looks at passive smoking in the context of the ARIC IMT data.

8.3. Other Pathophysiological Evidence

The 1997 report described evidence for pathophysiological mechanisms that may mediate the cardiovascular effects of ETS. Additional pathophysiological evidence is reviewed below.

8.3.1. Internal carotid artery thickness (IMT)

Results from the British Regional Heart Study (Ebrahim *et al.,* 1999) suggest that IMT of the common carotid artery is strongly associated with risk factors for stroke while IMT of the bifurcation was more directly associated with plaque and ischemic heart disease. It appeared that the presence of plaques rather than IMT *per se* was the more important predictor of disease risk. The presence of plaques was in turn significantly associated with increasing levels of fibrinogen in men ($P<0.01$ for trend), and to a lesser extent in women. ETS exposure was not evaluated in this study, however, Iso *et al.* (1996) found an association between fibrinogen levels and ETS exposure in women (see below).

8.3.2. Endothelial function

Several recent studies in humans and animals continue to document that ETS exposure damages vascular endothelium. This is usually manifested as impaired endothelium-dependent dilatation of coronary arteries. Woo *et al.* (2000) found significantly ($p<0.001$) diminished flow-mediated dilatation (FMD) in casino workers extensively exposed to ETS compared to unexposed controls. FMD was also observed by Raitakari *et al* (1999) to be significantly reduced in former passive ($P<0.01$) and current passive ($P<0.001$) smokers compared with unexposed nonsmokers. In a study by Sumida *et al.* (1998), acetylcholine (ACh) induced coronary artery dilatation in nonsmoking women but caused significant arterial constriction in women passively or actively exposed to smoke ($p<0.01$). Yet another measure of endothelial function, coronary flow velocity reserve, was found by Otsuka *et al.* (2001) to be significantly diminished ($p<0.001$) in young men following a 30 min exposure to passive smoke. In studies of atherogenesis in rabbits, secondhand smoke increased intimal lesion size in the aorta and inhibited ACh-induced relaxation of isolated aortic rings (Hutchison *et al.,* 1999). This effect may be mediated by ETS's ability to inhibit nitric oxide synthase and decrease endothelial arginine (Hutchison *et al.,* 2001). In both the human and animal studies, similar aortic responses in exposed and unexposed groups to endothelium-independent (nitroglycerin-induced) dilatation indicated that the endothelium is adversely affected by ETS exposure.

8.3.3. Exercise tolerance

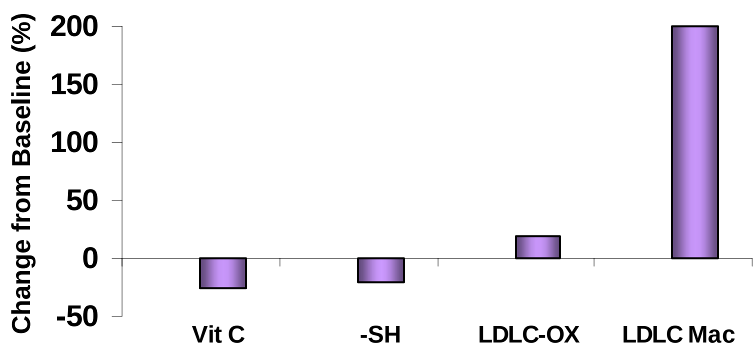
The deleterious effects of exposure to smoke and CO on oxygen transport and usage during exercise were recently reviewed by McDonough and Moffat (1999) but no data beyond those included in the 1997 report were identified by OEHHA staff.

8.3.4. Lipid profile

The growth of atherosclerotic plaques is associated with the accumulation of LDL-cholesterol (LDL-C) by macrophages, the precursors to foam cells in atherosclerotic lesions. Peroxidation of LDL-C also enhances its penetration of the arterial intima, binding to the extracellular matrix of intimal cells (Wang *et al.,* 2001), and uptake by macrophages. Valkonen and Kuusi (1998) examined the blood of nonsmokers prior to, and 1.5 and 6 hours after starting a 30-min exposure to ETS. They measured serum cholesterol, HDL-C, triglycerides and LDL-C levels, lipid- and aqueous-soluble antioxidants, and the combined ability of all antioxidants to resist artificially induced LDL-C peroxidation. Acute exposure to ETS resulted in a 25% decrease in serum ascorbic acid starting at 1.5 hrs after exposure and lasting 6 hrs ($P<0.001$), and a gradual decrease in sulfhydryls by 21% from baseline by 6 hrs ($P<0.063$) signifying a loss of antioxidant defenses. There was a concomitant 19% decrease in the resistance of LDL-C to Cu^{2+}-initiated oxidation. Uptake by cultured macrophages of LDL-C isolated following ETS exposure was found to be 1.6-2.3 times higher than that of unexposed LDL-C (Fig 8.09). Thus, ETS exposure enhanced peroxidation of LDL-C and its accumulation in macrophages, both of which occur during the formation of atherosclerotic plaques. In a subsequent study, peroxidation of LDL-C after ETS exposure was ameliorated by ascorbic acid administration (Valkonen & Kuusi, 2000), consistent with the role of peroxidation in plaque formation.

Whereas LDL-C promotes atherogenesis, HDL-C is protective and low HDL-C levels are considered a risk factor for CHD. In the study by Moskowitz *et al.* (1999), HDL-C levels in children with long-term passive smoke exposure were lower than in children from nonsmoking families (1.21 ± 0.26 vs 1.31 ± 0.26 mmol/L; $p \leq 0.01$). This difference was especially pronounced for the subfraction HDL_2-C (0.31 ± 0.18 vs 0.41± 0.19 mmol/L, trend $p \leq 0.001$). This subfraction accounts for most of the variation in HDL-C and, in families with low levels of HDL_2-C, is associated with more frequent CHD death (Bodurtha *et al.,* 1987).

Figure 8.09 Effect of ETS Exposure on Blood Anti-oxidants, Lipid Oxidation and Accumulation in Macrophages



fr. Valkonen and Kuusi, 1998

Vit C – ascorbic acid; -SH – protein sulfhydryls; LDL-OX – oxidized LDL

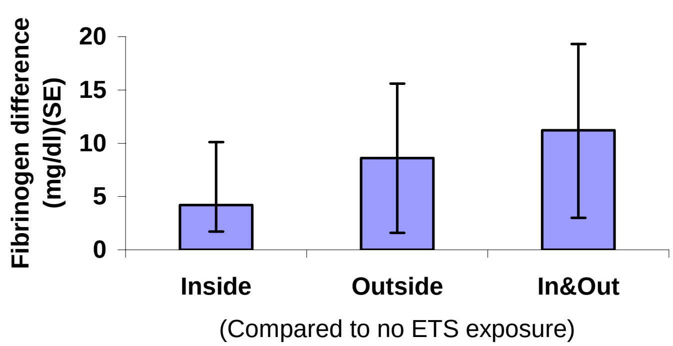
8.3.5. Platelet aggregation and endothelial damage

Activation of platelets is associated with damage to the lining of coronary arteries, and with the synthesis and secretion of thromboxanes, which in turn promote vasoconstriction and platelet aggregation. Levels of thromboxane in the blood are thus a measure of platelet activation and signal an increased likelihood of thrombus formation. The formation of thrombi may elevate the risk of an ischemic event such as myocardial infarction. Schmid *et al.* (1996) examined malondialdehyde (MDA), plasma and serum thromboxane B_2 (TXB_2), 11-dehydrothromboxane B_2, and conversion of exogenous arachidonic acid to TXB_2 and to hydroxy-5,8,10-heptadecatrienoic acid in 12 active smokers and 12 nonsmokers following exposure to ETS. For both groups, both single 60-min exposures and exposures repeated on 5 successive days resulted in significant increases ($p<0.05$) in all parameters except serum TXB_2. Whereas prior to acute smoke exposure, the levels of all six compounds were significantly lower ($p<0.5$) in nonsmokers than in smokers, after 4 days of ETS exposures, the MDA and serum TXB_2 levels in nonsmokers rose and became similar to those of active smokers. Among nonsmokers, levels of MDA and plasma (but not serum) TXB_2 remained elevated 6 hours after exposure. Thus the acute effects of ETS on platelet activation were more pronounced in nonsmokers than in smokers, possibly due to chronic activation of platelets in the latter group, and repeated ETS exposure made nonsmokers more like smokers in this respect.

8.3.6. Fibrinogen levels

Elevated plasma fibrinogen is an important coronary risk factor associated with both active and passive smoking. In a cross-sectional study of 1,780 Japanese women, Iso *et al.* (1996) reported that in women exposed to ETS outside the home, fibrinogen levels were 8.6 (95% CI 1.6-15.6) mg/dl higher than among non-exposed women. For ETS exposure in the home only, fibrinogen levels were 4.2 mg/dl (95% CI 1.7-10.1) higher, while in women exposed both in and outside the home, fibrinogen levels were 11.2 (95% CI 3.0-19.3) mg/dl higher than in non-exposed women (Fig. 8.10).

Figure 8.10 Increased Plasma Fibrinogen in Women Exposed to ETS Inside and/or Outside the Home



Adapted from Iso *et al.*, 1996

8.3.7. Animal studies

Knight-Lozano et al., 2002. $ApoE^{-/-}$ mice lack apolipoprotein E, a high-affinity ligand for lipoprotein receptors, and as a result have elevated levels of serum LDL-C and triglycerides, and develop atherosclerotic plaques in a manner similar to humans. $ApoE^{-/-}$ mice and the normocholesterolemic mouse strain, C57BL/6, were compared in this study of the effects of hypercholesterolemia and smoke exposure on atherosclerotic lesion formation and mitochondrial damage in cardiovascular tissue. Mice were exposed to second hand smoke (SHS; a surrogate for ETS) at 1 and 30 mg/m^3 total suspended particulates (TSP) or filtered air 6 hr/d, 5 d/wk for 42 days, or to air for 21 days followed by 21 days of SHS. Examination of the aortas of SHS-exposed (30 mg/m^3) compared to non-exposed ApoE$^{-/-}$ mice revealed a mean increase in lesion size of 76% at 21 days and 156% at 42 days. In contrast, no lesions were observed in the aortic sinus region of C57BL/6 mice in any exposure group. However, comparison of lipid staining with oil red O (which is used to visualize atherosclerotic lesions) in entire aortas from SHS-exposed vs non-exposed mice revealed a 4.5-fold increase in stained area for ApoE$^{-/-}$ mice ($p<0.05$), and 2.1- and 3.7-fold increases for C57BL/6 mice at 21 and 42 days respectively.

Quantitative polymerase chain reaction was used to assess damage to aortic mitochondrial DNA. At both high (30 mg/m^3) and low (1 mg/m^3) TSP, significant mitochondrial damage was observed for both mouse strains. This effect was more pronounced in the ApoE$^{-/-}$ than the C57BL/6 mice, suggesting an interaction between hypercholesterolemia and SHS exposure ($p<0.001$). While higher or longer exposures caused substantially more mitochondrial damage ($p<0.001$), even the more environmentally relevant dose (1 mg/m^3) resulted in statistically significant damage ($p<0.001$). Mitochondrial damage could affect cardiovascular cell function through the increased formation of reactive nitrogen and oxygen species. These radicals can in turn oxidize LDL, which enhances its uptake into atherosclerotic plaques, and damage mitochondrial proteins, thereby disrupting energy production and intracellular signaling. These results are consistent with the view that oxidative stress mediates the link between ETS and cardiovascular disease.

Gairola et al., 2001. As described above, ApoE$^{-/-}$ mice develop atherosclerotic lesions very similar to those seen in human disease, including the formation of fatty streaks and fibrolipid lesions. In this study, female ApoE$^{-/-}$ mice (8-9 wks old) were fed a modified diet containing 21% w/w saturated fat and 0.15% w/w cholesterol, and then divided into control and sidestream smoke (SS) exposed groups. Animals were exposed to SS at 25 mg/m^3 particulates for 6 h/d, 5d/wk for 7 (9 exp, 9 ctrl), 10 (7 exp, 8 ctrl) or 14 (10 exp, 10 ctrl) weeks. Upon sacrifice the intimal surfaces along the arch, thoracic and abdominal sections of the aortas were examined microscopically for lesions. Images of lesions were captured digitally and the areas quantified with scanning software. The lipid content of aortic tissues was also measured. Atherosclerotic lesions covered greater areas in SS-exposed mice compared to controls starting at the earliest time (7 weeks) with a significantly more rapid increase in size through 14 weeks. This was especially pronounced in the thoracic region of the aorta, which in this model is not normally a lesion-susceptible area. In SS-exposed animals, 33 ± 11% of the intima was covered by lesions versus 10 ± 8% in controls ($P<0.001$). The lesions were also thicker in the SS mice as verified by an increase in esterified and unesterified cholesterol in these tissues. Macrophages were the predominant cellular component of the lesions. Exposure to SS was also associated with a modest, but statistically significant, transient increase in plasma cholesterol levels at 7 weeks (SS, 718 ± 61 vs Ctrl, 553 ± 26 mg/dl; $p=0.027$) that was not evident at the later time points. This transient increase may have been related to the increase in atherosclerosis in the SS-exposed group.

How well this study reflects realistic human ETS exposure conditions is questionable as the mice in this study were exposed to relatively high levels of smoke constituents, roughly ten times the respirable particulates in a smoky bar (Anderson *et al.*, 1991). However, even the most prolonged exposure was for only approximately 10% of their normal life spans. Although it may be that the cardiovascular consequences of brief intensive ETS exposure are different from those associated with chronic low-level ETS, in this animal model intense exposure was clearly associated with promotion of atherosclerosis.

8.4. Chapter summary and conclusions

The growing body of evidence continues to support the observation in the 1997 OEHHA document that chronic ETS exposure is causally associated with an increased risk for cardiovascular disease in the range of 20-50%. Ultimately, disease manifestation is the result of multiple, interrelated changes in the cardiovascular system. The ability of ETS to damage the arterial endothelium, as seen in loss of arterial elasticity and decreased endothelial responsiveness to endogenous signals, is well supported. Whether this damage leads directly to plaque formation has yet to be established, but the ability of ETS to promote plaque growth is evident from both human and animal studies. A mechanistic basis for ETS's atherogenic effects is provided by observations of ETS-associated decreases in HDL-C, increases in peroxidized LDL, compromised antioxidant defenses, and mitochondrial damage after ETS exposure. In addition, ETS is associated with platelet activation and elevated fibrinogen levels that in turn are associated with endothelial damage and plaque formation, respectively. These effects of ETS may also contribute to stroke, the etiology of which includes atherosclerosis of the carotid and large arteries of the brain, and degeneration of intracerebral arteries. Research in this area suggests that chronic ETS exposure increases the risk of stroke by about 82% (Bonita *et al.*, 1999).

In California in 1999, an estimated 81.7% of the adult population (or 19,530,547 persons ≥ 18 years of age) were nonsmokers according to the 1999 California Tobacco Survey (Gilpin *et al.*, 2001). Of this group, 12.75% (2,490,145) were exposed to ETS at work and/or at home during the two weeks preceding the survey. In this group, 8.19% (203,943) were exposed at work but not at home, 4.32% (107,574) were exposed at home but not at work, and 0.65% (16,186) were exposed in both locations (Gilpin, pers comm). Assuming these exposure patterns were stable over time, it is possible to calculate the number of cardiac deaths associated with exposure to ETS.

During 1999, in California there were 72,360 cardiac deaths (CDC, 2002b). As stated above, the data suggest that the risk (OR) for cardiovascular disease associated with ETS is in the range of 1.2-1.5. The population attributable risk (PAR) may be calculated from the formula: PAR = p(OR-1)/p(OR-1)+1, where p is the portion of the nonsmoking population exposed to ETS. For nonsmoking indoor workers exposed at home, the lower OR of 1.2 gives an attributable risk of 0.009 [0.043*(1.2-1)]/[0.043*(1.2-1)+1 = 0.009], and the upper OR of 1.5 gives 0.021 [0.043*(1.5-1)]/ [0.043*(1.5-1)+1 = 0.021]. Thus the PAR is in the range of 0.9-2.1%. A similar range (0.7-2.8%) was found by de Groh and Morrison (2002) in Canada for CHD deaths and ETS at home. For cardiac death in California in 1999, this translates into 651 – 1,520 excess deaths attributable to ETS exposure if all ETS-associated cardiac deaths were from home exposure only.

Similarly, the PAR for cardiac death associated with workplace ETS was 1.4-3.9% (assuming 8.19% of workers were routinely exposed to ETS and an OR range of 1.2-1.5). This range for PAR compares favorably with the approximate attributable fraction of 4% calculated by Steenland (1999) for cardiac death from ETS at work. Thus among the estimated 1,616,054 indoor workers exposed to ETS only at work in 1999 (Gilpin *et al.*, 2002), there would have been an additional 1,013-2,822 cardiac deaths attributable to ETS.

These estimates may be high as they are based on any ETS exposure and exposure intensities were not determined. On the other hand they exclude other ETS exposures outside of work or home, such as in vehicles and in other environments, and they exclude outdoor workers. Thus the actual number of exposed persons and ETS exposure levels may be higher. Of the individuals exposed at work, 0.65% were among those reportedly also exposed at home. This overlap would slightly decrease the total number of individuals exposed to any ETS but increase the individual risk of adverse effects (He *et al.*, 1999).

Thus recent research continues to indicate that ETS exposure increases the risk of cardiovascular disease and stroke. It is also evident that these effects exacerbate or are exacerbated by underlying conditions, and individuals with other chronic conditions such as diabetes, vascular disease or hypertension comprise a susceptible population at even greater risk from ETS exposure.

8.5. References

Anderson R, Theron AJ, Richards GA, Myer MS, van Rensburg AJ (1991). Passive smoking by humans sensitizes circulating neutrophils. Am Rev Respir Dis 144(3 Pt 1):570-4.

Bodurtha JN, Schieken R, Segrest J, Nance WE (1987). High-density lipoprotein-cholesterol subfractions in adolescent twins. Pediatrics 79(2):181-9.

Bonita R, Duncan J, Truelsen T, Jackson RT, Beaglehole R (1999). Passive smoking as well as active smoking increases the risk of acute stroke. Tob Control 8(2):156-60.

Bots ML, Hoes AW, Hofman A, Witteman JC, Grobbee DE (1999). Cross-sectionally assessed carotid intima-media thickness relates to long-term risk of stroke, coronary heart disease and death as estimated by available risk functions. J Intern Med 245(3):269-76.

Brown KS (1998). The risk of coronary heart disease in non-smokers exposed to environmental tobacco smoke: a rejoinder to Gross. Environmetrics 9:213-21.

Butler T (1988). The relationship of passive smoking to various health outcomes among Seventh-day Adventists in California. [Doctoral dissertation, University of California, Los Angeles].

Cal EPA (1997). Health effects of exposure to environmental tobacco smoke. Sacramento, California: Office of Environmental Health Hazard Assessment.

Chambless LE, Folsom AR, Clegg LX, Sharrett AR, Shahar E, Nieto FJ, Rosamond WD, Evans G (2000). Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol 151(5):478-87.

Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, Clegg LX (1997). Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. Am J Epidemiol 146(6):483-94.

Chamuleau SA, Tio RA, de Cock CC, de Muinck ED, Pijls NH, van Eck-Smit BL, *et al.* (2002). Prognostic value of coronary blood flow velocity and myocardial perfusion in intermediate coronary narrowings and multivessel disease. J Am Coll Cardiol 39(5):852-8.

Ciruzzi M, Pramparo P, Esteban O, Rozlosnik J, Tartaglione J, Abecasis B, Cesar J, De Rosa J, Paterno C, Schargrodsky H (1998). Case-control study of passive smoking at home and risk of acute myocardial infarction. Argentine FRICAS Investigators. Factores de Riesgo Coronario en America del Sur. J Am Coll Cardiol 31(4):797-803.

Claeys MJ, Vrints CJ, Bosmans J, Krug B, Blocks PP, Snoeck JP (1996). Coronary flow reserve during coronary angioplasty in patients with recent myocardial infarction: relation to stenosis and myocardial viability. J Am Coll Cardiol 28(7):1712-9.

de Groh M, Morrison HI (2002). Environmental tobacco smoke and deaths from coronary heart disease in Canada. Chronic Dis Can 23(1):13-6.

Dobson AJ, Alexander HM, Heller RF, Lloyd DM (1991). Passive smoking and the risk of heart attack or coronary death. Med J Aust 154(12):793-7.

Ebrahim S, Papacosta O, Whincup P, Wannamethee G, Walker M, Nicolaides AN, *et al*. (1999). Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British Regional Heart Study. Stroke 30(4):841-50.

Elwood PC, Beswick A, Pickering J, McCarron P, O'Brien JR, Renaud SR, Flower RJ (2001). Platelet tests in the prediction of myocardial infarction and ischaemic stroke: evidence from the Caerphilly Prospective Study. Br J Haematol 113(2):514-20.

Elwood PC, Renaud S, Sharp DS, Beswick AD, O'Brien JR, Yarnell JW (1991). Ischemic heart disease and platelet aggregation. The Caerphilly Collaborative Heart Disease Study. Circulation 83(1):38-44.

Enstrom JE, Kabat GC (2003). Environmental tobacco smoke and tobacco related mortality ina prospective study of Californians, 19600-98. Br Med J 326(7398):1057-66.

Forastiere F, Mallone S, Lo Presti E, Baldacci S, Pistelli F, Simoni M, *et al.* (2000). Characteristics of nonsmoking women exposed to spouses who smoke: epidemiologic study on environment and health in women from four Italian areas. Environ Health Perspect 108(12):1171-7.

Gairola CG, Drawdy ML, Block AE, Daugherty A (2001). Sidestream cigarette smoke accelerates atherogenesis in apolipoprotein E-/- mice. Atherosclerosis 156(1):49-55.

Garland C, Barrett-Connor E, Suarez L, Criqui MH, Wingard DL (1985). Effects of passive smoking on ischemic heart disease mortality of nonsmokers. A prospective study. Am J Epidemiol 121(5):645-50.

Gilpin E, Emery S, Farkas A, Distefan J, White M, Pierce J (2001) (Cancer prevention and control program, University of California, San Diego). The California Tobacco Control Program; a decade of progress, results from the California tobacco survey, 1990-1999. California Dept. Health Services.

Gilpin EA, Farkas AJ, Emery SL, Ake CF, Pierce JP (2002). Clean indoor air: advances in California, 1990-1999. Am J Pub Health (92(5)785-91.

He J, Vupputuri S, Allen K, Prerost MR, Hughes J, Whelton PK (1999). Passive smoking and the risk of coronary heart disease--a meta-analysis of epidemiologic studies. N Engl J Med 340(12):920-6.

He Y (1989). [Women's passive smoking and coronary heart disease]. Zhonghua Yu Fang Yi Xue Za Zhi 23(1):19-22.

He Y, Lam TH, Li LS, Li LS, Du RY, Jia GL, Huang JY, Zheng JS (1994). Passive smoking at work as a risk factor for coronary heart disease in Chinese women who have never smoked. BMJ 308(6925):380-4.

Hirayama T (1990). Passive smoking. N Z Med J 103(883):54.

Hole DJ, Gillis CR, Chopra C, Hawthorne VM (1989). Passive smoking and cardiorespiratory health in a general population in the west of Scotland. BMJ 299(6696):423-7.

Howard G, Wagenknecht LE, Burke GL, Diez-Roux A, Evans GW, McGovern P, Nieto FJ, Tell GS (1998). Cigarette smoking and progression of atherosclerosis: The Atherosclerosis Risk in Communities (ARIC) Study. JAMA 279(2):119-24.

Hozumi T, Yoshida K, Ogata Y, Akasaka T, Asami Y, Takagi T, Morioka S (1998). Noninvasive assessment of significant left anterior descending coronary artery stenosis by coronary flow velocity reserve with transthoracic color Doppler echocardiography. Circulation 97(16):1557-62.

Humble C, Croft J, Gerber A, Casper M, Hames CG, Tyroler HA (1990). Passive smoking and 20-year cardiovascular disease mortality among nonsmoking wives, Evans County, Georgia. Am J Public Health 80(5):599-601.

Hutchison SJ, Sievers RE, Zhu BQ, Sun YP, Stewart DJ, Parmley WW, Chatterjee K (2001). Secondhand tobacco smoke impairs rabbit pulmonary artery endothelium- dependent relaxation. Chest 120(6):2004-12.

Hutchison SJ, Sudhir K, Sievers RE, Zhu BQ, Sun YP, Chou TM, *et al*. (1999). Effects of L-arginine on atherogenesis and endothelial dysfunction due to secondhand smoke. Hypertension 34(1):44-50.

Iso H, Shimamoto T, Sato S, Koike K, Iida M, Komachi Y (1996). Passive smoking and plasma fibrinogen concentrations. Am J Epidemiol 144(12):1151-4.

Jackson R (1989). The Auckland Heart Study: a case-control study of coronary heart disease. [Auckland, New Zealand: Doctoral thesis, university of Auckland].

Kawachi I, Colditz GA, Speizer FE, Manson JE, Stampfer MJ, Willett WC, Hennekens CH (1997). A prospective study of passive smoking and coronary heart disease. Circulation 95(10):2374-9.

Knight-Lozano CA, Young CG, Burow DL, Hu ZY, Uyeminami D, Pinkerton KE, Ischiropoulos H, Ballinger SW (2002). Cigarette smoke exposure and hypercholesterolemia increase mitochondrial damage in cardiovascular tissues. Circulation 105(7):849-54.

La Vecchia C, D'Avanzo B, Franzosi MG, Tognoni G (1993). Passive smoking and the risk of acute myocardial infarction GISSI-EFRIM investigations. Lancet 341(8843):505-6.

Law MR, Morris JK, Wald NJ (1997). Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. BMJ 315(7114):973-80.

Layard MW (1995). Ischemic heart disease and spousal smoking in the National Mortality Followback Survey. Regul Toxicol Pharmacol 21(1):180-3.

Lee PN, Chamberlain J, Alderson MR (1986). Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. Br J Cancer 54(1):97-105.

LeVois ME, Layard MW (1995). Publication bias in the environmental tobacco smoke/coronary heart disease epidemiologic literature. Regul Toxicol Pharmacol 21(1):184-91 (REF: 55).

McDonough P, Moffatt RJ (1999). Smoking-induced elevations in blood carboxyhaemoglobin levels. Effect on maximal oxygen uptake. Sports Med 27(5):275-83.

Moskowitz WB, Schwartz PF, Schieken RM (1999). Childhood passive smoking, race, and coronary artery disease risk: the MCV Twin Study. Medical College of Virginia. Arch Pediatr Adolesc Med 153(5):446-53.

Muscat JE, Wynder EL (1995). Exposure to environmental tobacco smoke and the risk of heart attack. Int J Epidemiol 24(4):715-9.

Neunteufl T, Katzenschlager R, Hassan A, Klaar U, Schwarzacher S, Glogar D, Bauer P, Weidinger F (1997). Systemic endothelial dysfunction is related to the extent and severity of coronary artery disease. Atherosclerosis 129(1):111-8.

Nolan J, Batin PD, Andrews R, Lindsay SJ, Brooksby P, Mullen M, *et al.* (1998). Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). Circulation 98(15):1510-6.

Nyberg F, Agudo A, Boffetta P, Fortes C, Gonzalez CA, Pershagen G (1998). A European validation study of smoking and environmental tobacco smoke exposure in nonsmoking lung cancer cases and controls. Cancer Causes Control 9(2):173-82.

Nyberg F, Isaksson I, Harris JR, Pershagen G (1997). Misclassification of smoking status and lung cancer risk from environmental tobacco smoke in never-smokers. Epidemiology 8(3):304-9.

Otsuka R, Watanabe H, Hirata K, Tokai K, Muro T, Yoshiyama M, Takeuchi K, Yoshikawa J (2001). Acute effects of passive smoking on the coronary circulation in healthy young adults. JAMA 286(4):436-41.

Pope CA 3rd, Eatough DJ, Gold DR, Pang Y, Nielsen KR, Naith P, Verrier RL, Kanner RE (2001). Acute exposure to environmental tobacco smoke and heart rate variability. Environ Health Perspect 109(7):711-6.

Raitakari OT, Adams MR, McCredie RJ, Griffiths KA, Celermajer DS (1999). Arterial endothelial dysfunction related to passive smoking is potentially reversible in healthy young adults. Ann Intern Med 130(7):578-81.

Rosenlund M, Berglind N, Gustavsson A, Reuterwall C, Hallqvist J, Nyberg F, Pershagen G (2001). Environmental tobacco smoke and myocardial infarction among never- smokers in the Stockholm Heart Epidemiology Program (SHEEP). Epidemiology 12(5):558-64.

Sandler DP, Comstock GW, Helsing KJ, Shore DL (1989). Deaths from all causes in non-smokers who lived with smokers. Am J Public Health 79(2):163-7.

Schmid P, Karanikas G, Kritz H, Pirich C, Stamatopoulos Y, Peskar BA, Sinzinger H (1996). Passive smoking and platelet thromboxane. Thromb Res 81(4):451-60.

Steenland K, Thun M, Lally C, Heath C Jr (1996). Environmental tobacco smoke and coronary heart disease in the American Cancer Society CPS-II cohort. Circulation 94(4):622-8.

Stefanadis C, Vlachopoulos C, Tsiamis E, Diamantopoulos L, Toutouzas K, Giatrakos N, *et al*. (1998). Unfavorable effects of passive smoking on aortic function in men. Ann Intern Med 128(6):426-34.

Sumida H, Watanabe H, Kugiyama K, Ohgushi M, Matsumura T, Yasue H (1998). Does passive smoking impair endothelium-dependent coronary artery dilation in women? J Am Coll Cardiol 31(4):811-5.

Svendsen KH, Kuller LH, Martin MJ, Ockene JK (1987). Effects of passive smoking in the Multiple Risk Factor Intervention Trial. Am J Epidemiol 126(5):783-95.

Tanaka T, Oka Y, Tawara I, Sada T, Kira Y (1998). Acute effects of nicotine content in cigarettes on coronary flow velocity and coronary flow reserve in men. Am J Cardiol 82(10):1275-8, A9.

Tunstall-Pedoe H, Brown CA, Woodward M, Tavendale R (1995). Passive smoking by self report and serum cotinine and the prevalence of respiratory and coronary heart disease in the Scottish heart health study. J Epidemiol Community Health 49(2):139-43.

U.S.-DHHS U.S. Department of Health and Human Services (1990). U.S. Public Health Service: The Health

Benefits of Smoking Cessation. A Report of the Surgeon General. DHHS (CDC) . Report No.: 90-8416.

Valkonen M, Kuusi T (1998). Passive smoking induces atherogenic changes in low-density lipoprotein. Circulation 97(20):2012-6.

Valkonen MM, Kuusi T (2000). Vitamin C prevents the acute atherogenic effects of passive smoking. Free Radic Biol Med 28(3):428-36.

Wang X, Greilberger J, Ratschek M, Jurgens G (2001). Oxidative modifications of LDL increase its binding to extracellular matrix from human aortic intima: influence of lesion development, lipoprotein lipase and calcium. J Pathol 195(2):244-50.

Wells AJ (1998). Heart disease from passive smoking in the workplace. J Am Coll Cardiol 31(1):1-9.

Woo KS, Chook P, Leong HC, Huang XS, Celermajer DS (2000). The impact of heavy passive smoking on arterial endothelial function in modernized Chinese. J Am Coll Cardiol 36(4):1228-32.

You RX, Thrift AG, McNeil JJ, Davis SM, Donnan GA (1999). Ischemic stroke risk and passive exposure to spouses' cigarette smoking. Melbourne Stroke Risk Factor Study (MERFS) Group. Am J Public Health 89(4):572-5.